O‘ZBEKISTON RESPUBLIKASI OLIY VA O‘RTA MAXSUS TA’LIM VAZIRLIGI

SAMARQAND DAVLAT UNIVERSITETI

BIOLOGIYA VA KIMYO FAKULTETI KIMYO BO‘LIMI

ORGANIK VA NOORGANIK KIMYO KAFEDRASI

“3,4-Dimektoksi-β-feniletilaminning nikotin kislotasi bilan kondensatlanish va sikllanish reaksiyasi”

BITIRUV MALAKAVIY ISHI

Bajardi: “Kimyo” ta’lim yo‘nalishi bitiruvchisi Ubaydullayev A.U.

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ILMIY RAXBAR:
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Bitiruv malakaviy ishi kafedradan dastlabki himoyadan o‘tdi.
_____ sonli bayonnomasi “_____” _____2017 yil

Samarqand – 2017

MUNDARIJA

I. KIRISH

Bitiruv ishi mavzusining dolzarbligi. Turli sohalarda qo‘llaniladigan piridin va uning qisman yoki to‘liq gidrogenlangan analoglari kimyosi kimyogarlar va farmakologlarda katta qiziqish uyg‘otadi. Piridinli, pipiridinli va tetragidroizoxinolinli halqalar ko‘pchilik tabiiy va sintitik biologik faol moddalarning asosiy fragmenti hisoblanadi. To‘rtlamchi piridiniy tuzlari alkilovchi agentlar, fazolararo ko‘chish katalizatorlari, antiseptiklar, ionli suyuqliklar sirt faol va antikarozion vositalar sifatida qo‘llaniladi.

Ma’lumki, izoxinolinning juda ko‘p hosilalari turli biologik faollikni namoyon etadi. Ularning ayrimlari turli kilinik sinov bosqichlariga kiritilgan yoki dorilar ko‘rinishida foydalaniladi. Bundan tashqari izoxinolin yadrosi muhim alkaloidlar tarkibiga kiradi. Shuning uchun potensial biologik faolliklarni namoyon qiluvchi izoxinolin yadrosiga ega yangi birikmalar izlash asosiy maqsadlarimizdan hisoblanadi.

Shu nuqtai nazardan aromatik yadroga yangi farmokofor fragmentlarni kiritish, ularni modifikatsiyalash usullari, olingan moddalar analizini o‘tkazish bir nechta uglerod atomlarini azot atomlariga almashtirish kabilar katta qiziqish uyg‘otadi.

Bitiruv malakaviy ishi mavzusining maqsadi. 6,7-Dimetoksi-1-(piridin-3-il)-1,2,3,4-tetragidroizoxinolinni kondensatlanish va sikllanish reaksiyasi asosida sintez qilish, olingan birikmalarning tuzilishini fizik – kimyoviy usullar yordamida o‘rganish.

Tadqiqotning ilmiy yangiligi. Ilk marotaba 6,7-Dimetoksi-1-(piridin-3-il)-1,2,3,4-tetragidroizoxinolin sintez qilindi va ular sintezining muqobil sharoitlari topildi. Reaksiyalar yo‘nalishi va qonuniyatlari aniqlandi.

Tadqiqotning amaliy ahamiyati. Bitiruv malakaviy ishining ahamiyati shundan iboratki, 6,7-dimetoksi-1-(piridin-3-il)-1,2,3,4-tetragidroizoxinolinni kondensatlanish va sikllanish reaksiyasi asosida sintezi to‘g‘risida adabiyotlarda ma’lumotlar yo‘q. Shu tufayli bu reaksiyalardan olingan har bir natija nazariy organik kimyo fani uchun yangi ma’lumot hisoblanadi. Olingan mahsulot PASS dasturiga

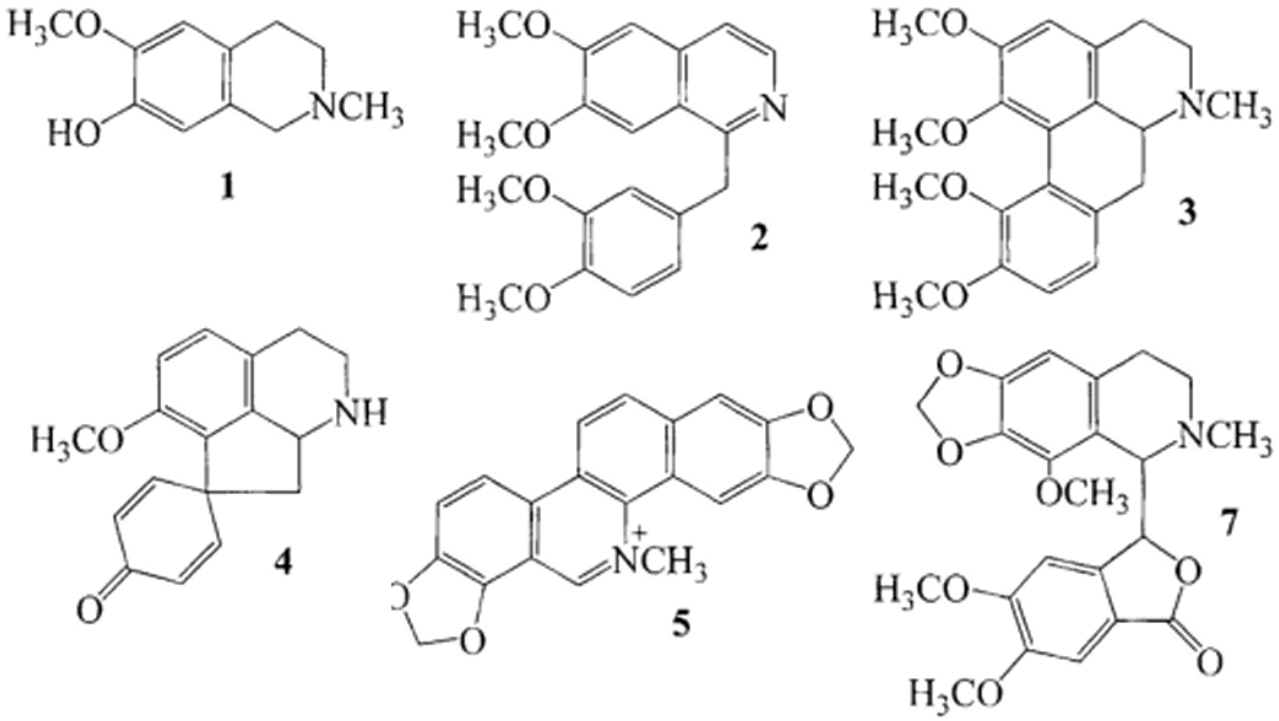
asosan, muhim farmakologik faollikka egaligi aniqlandi. Bu esa olib borilgan sintezning ham nazariy, ham amaliy jihatdan muhimligini bildiradi.

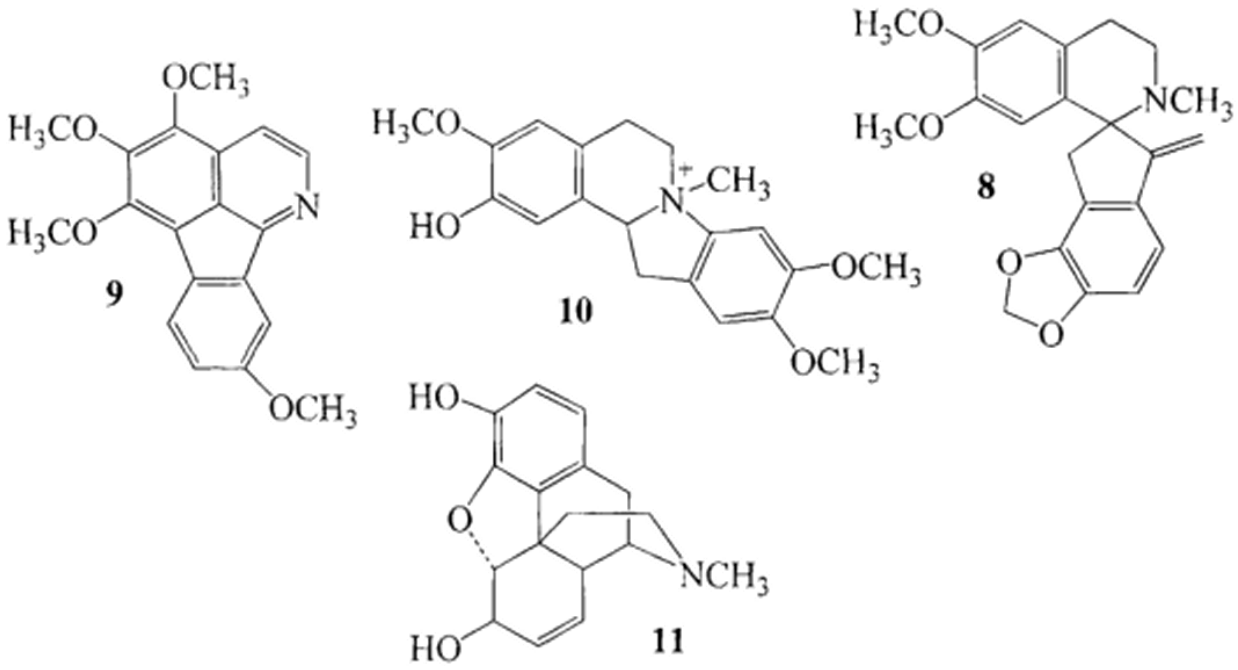
Bajarilgan ishlar “Organik va noorganik kimyo” kafedrasi hamda O‘zFA O‘simlik moddalar kimyosi institutining (Toshkent) “Alkaloidlar kimyosi” laboratoriyasida katta ilmiy xodim k.f.n. V.I.Vinogradova rahbarligida olib borildi.

II. ADABIYOTLAR SHARHI

2.1. Alkolidlar va doiri vositalar - izoxinolin hosilalarining umumiy tafsifi

Hozirgi vaqtda izoxinolin alkaloidlari yaxshi o‘rganilgan va mingdan ortiq vakillari sanab o‘tiladi [1-5]. Ular tabiatda keng tarqalgan (40 dan ortiq o‘simlik oilalari vakillarida topilgan). Ko‘knordoshlar, barbarislar, lavlagidoshlar, magnoliyadoshlar, oilalari o‘simliklari ularga ancha boy. O‘simliklarda izoxinolin halqasi fenilalanin va tirozin aminokislatalaridan hosil bo‘ladi. Izoxinolin alkaloidlari quydagi asosiy guruhlarga bo‘linadi. Oddiy izoxinolinlar (koripallin 1), benzylizoxinolinlar (papaverin 2), aparfinlar (gloutsin 3), proaporfinlar (prouusiferin 4), protoberberinlar (berbern), benzofenantridinlar (sangvinarin5), pavinlar (argemonin 6), ftalidizoxinolinlar (norkotin 7), spirobenzilizoxinolinlar (oxotensimin 8), 2-benzilizoxinolinlar, 1-fenil va 4-feniltetragidroizoxinolinlar, azofluorantenlar (rufessin 9), dibenzopirrokollinlar (kriptaustolin 10), fenantrinizoxinolinlar (morfin 11) va b.q.lar.





Izoxinolin alkoloidli o‘simliklar muhim dorivor ahamiyatga ega. Ulardan ayrimlari tibbiyotda qo‘llaniladi. Masalan: kodein – yo‘talga qarshi vosita, morfin – narkotik analgetik, tubokurarin – miorelaksant, emitin – qayt qildiruvchi, antiparazitar, papaverin – qon tomirlarini kengaytiruvchi va antigipertinziv vosita.

Ko‘pchilik sintetik va yarim sintetik moddalar preparatning asosiy ta’sir xossasini o‘zgartirish yoki kuchaytirish, nojo‘ya ta’sirlarni kamaytirish maqsadida ishlab chiqilgan alkaloidlarning struktur modifikatsiyalari hisoblanadi [6,7]. Masalan opiod reseptorlari antagonistinaloksan opiy alkaloidi tebain asosida ishlab chiqilgan bo‘lib u azot atomida alkil yoki boshqa radikal ham tutishi mumkin. Asosiy farqi 14 holatdagi gidroksil guruhi o‘rniga oksoguruhning bo‘lishidir. Bu esa naloksanda morfinga o‘xshash ta’sir yo‘qolishiga olib kelgan. U bog‘langan antogonistlar yoki opioidli reseptorlar bilan bog‘lanib, raqobatli antegonizm tipi bo‘yicha ta’sir qiladi. Kodein – morfinning metil hosilasi. Ta’sir xarakteri bo‘yicha kodein morfinga yaqin, lekin og‘riq qoldiruvchi xossasi kamroq, yo‘tal markazi qo‘zg‘alishini kamaytirish qobilyati kuchliroq ifodalangan. Morfinga nisbatdan oshqozon-ichak trakti faoliyatini kamroq tormozlaydi.

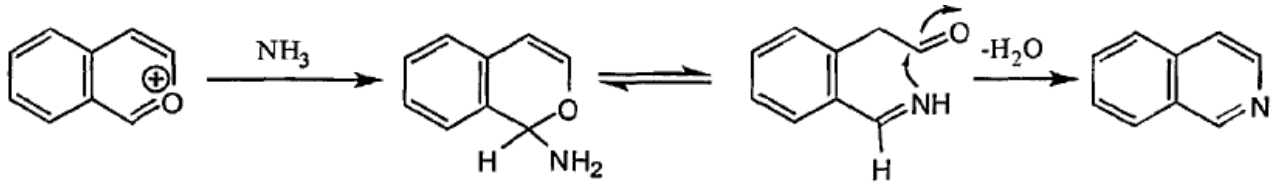
Izoxinolin kimyosi sohasida fundamental sharhlar va monografiyalarning ko‘pligi bu sinf birikmalari katta qiziqishga ega ekanligini anglatadi [2,3-20]. Bunday

birikmalarning kimyoviy va formakologik xossalarini o‘rganish hozirgi vaqtgacha dolzarb bo‘lib qolmoqda.

2.2. Izoxinolin yadrosi sintez usullari

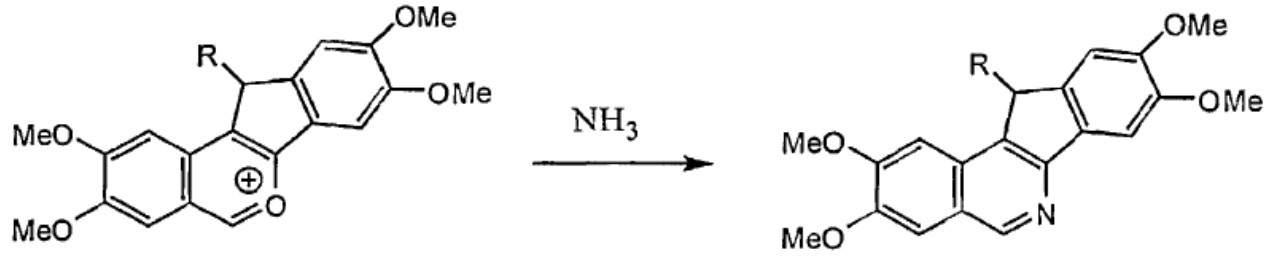
2.2.1. Izokumorin hosilalari va benzo[c]piriliy tuzlaridagi geteroatomni almashtirish stemalari

Piriliy tuzlari geteroaril sistemalar sintezida muhim ro‘l o‘ynaydi. Bunga ikkinchi benzopiriliy molekulasida kislorod atomini azotga aylantirib izoxinolin olish reaksiyasiga misol bo‘la oladi [5]. Reaksiya ANRORC-mexanizimida boradi.

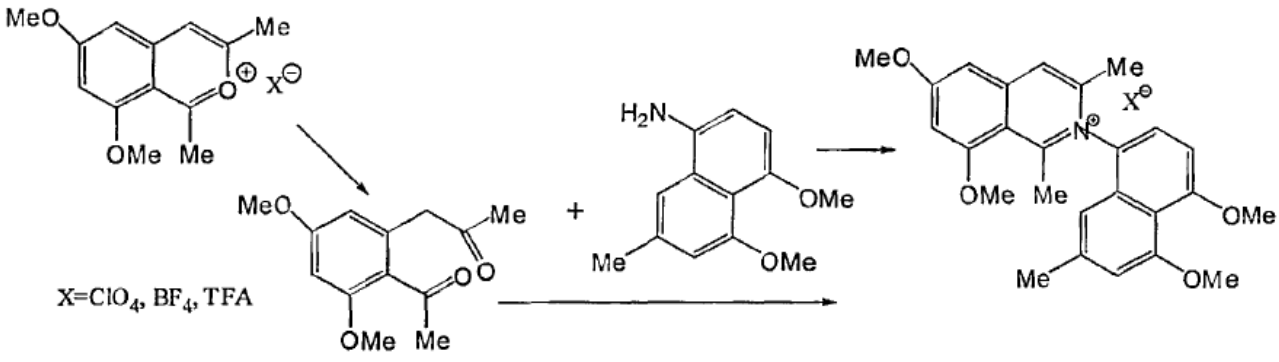


Reksiyada geterosiklik fragment holati bo‘yicha qo‘shni manfiy zaryadli kislorod atomiga nukleofil agent birikadi.

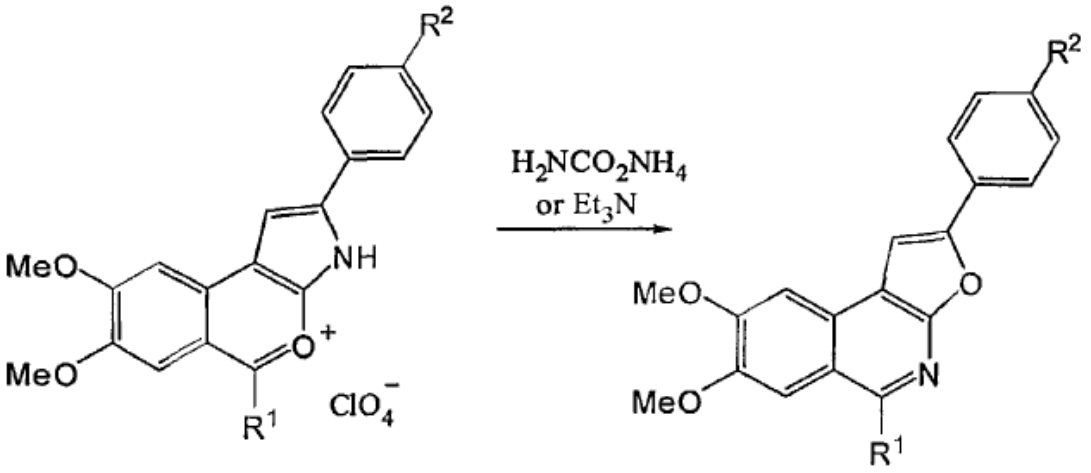
Shunga o‘xshash usulda 4,5,8,9-tatrametoksi-11-aril-H-indeno[1,2-c]-2-benzopiriliy tuziga ammiak ta’sir ettirib indeno[1,2-c] izoxinolin olingan [6].



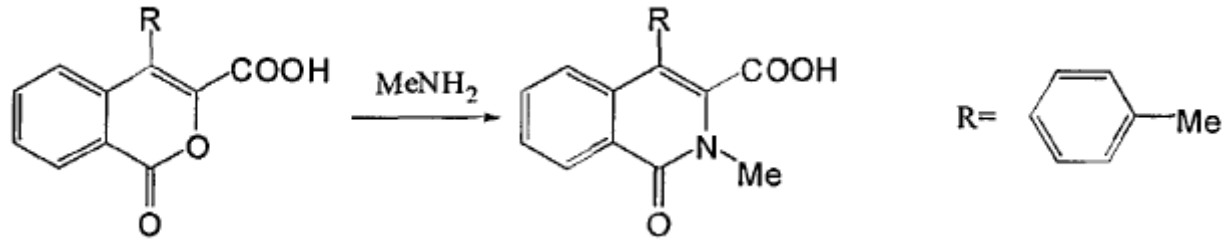
Mos benzopiriliy tuzi yoki siklik diketonning suvli ammiak bilan reaksiyasidan N-almashinmagan izoxinolin strukturasi hosil bo‘ladi.Bunda aminning ta’siri bilan bir vaqtda azot atomiga o‘rinbosar kiritiladi [7].



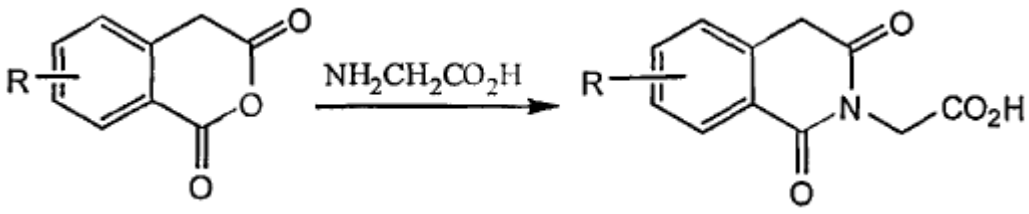
Maqolada noodatiy N/O ga O/N qo‘sh ichkimolekulyar resikilizatsiyasi o‘tkazilgan. Natijada pirrol piriliy perxloratlaridan furo[2,3-*c*]izoxinolinlar hosil bo‘lishi kuzatilgan [8].



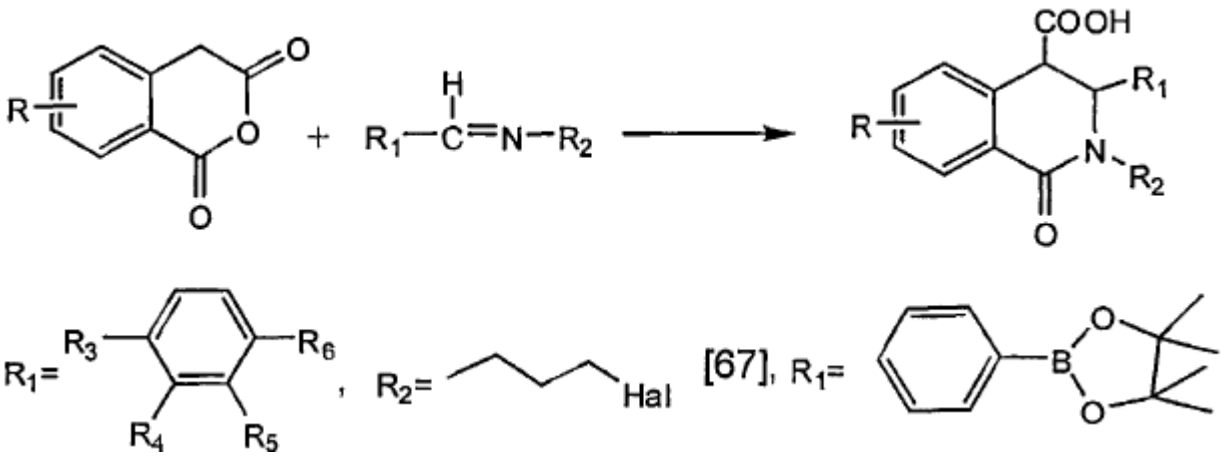
Avval piriliy halqasi ochilgan natijada unga nukleofillar hujum qilgan. So‘ngra azot atomining qo‘shni pirrol halqasi bilan ichkimolekulyar tutashishidan piridin yadrosi sikllangan.kislorodning piriliy halqasi bilan qo‘shilishidan furan halqasi hosil bo‘lgan.Izokumorin xosilalar ammiak yoki birlamchi aminlarning suvli yoki spirtli eritmasi ta’sirida izokorostrilga aylanadi. Izokumorin uchinchi holatda korboksilgurihining bo‘lishi faqatgina kislorod atomining birlamchi amin ta’sirida azotga almashishiga halaqit berib qolmasdan c(3)da –COOH bo‘lgan izokorbostrillar olishga imkon beradi [9].



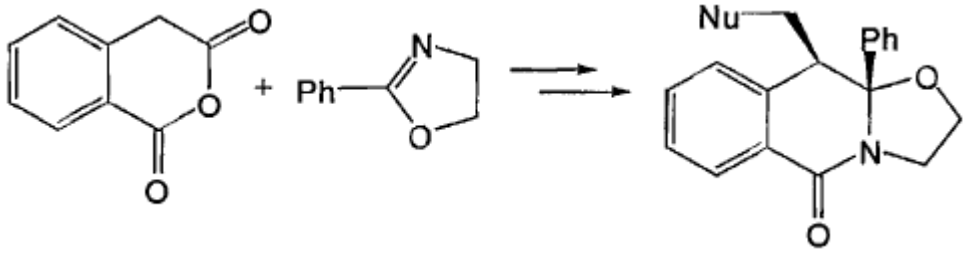
Birlamchi aminlarga gomofital angidrid ta’siridan izokorbostinlar hosil bo‘ladi. Azot tutgan komponent sifatida turli xil birlamchi aminlarni tanlash azot atomida turli xil o‘rinbosarlari bo‘lgan izoxinolinlarni olishga imkon beradi [10].



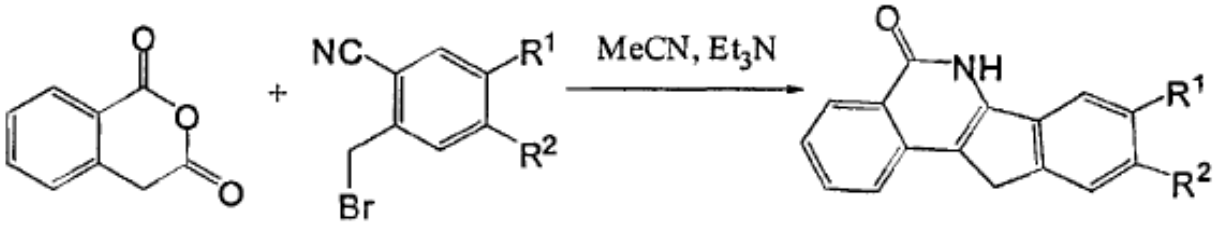
Shiff asoslari bilan gomoftalar aldegidning ta’sirlashuvi c(3) atomi va azot atomida o‘rinbosar tutgan 4-izoxinolin kislotani olishga imkon beradi [11].



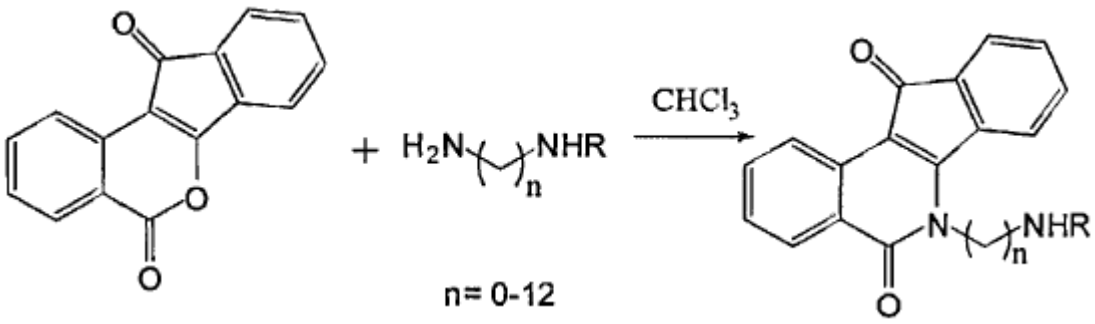
Siklik Shiff asosi 4,5-digidro-2-fenil-1,3-oksazol furan halqasi bilan _____ tetrogidroizoxinolinni hosil qiladi [12].



Gomoftalar angidridning 2-brommetilbenzonitril bilan ta’sirlashuvidan indeno [1,2-c] izoxinolin-5-on-lar olingan [13].



Diaminoalkanlarning benzindeno [1,2-c] piran-5-11-dionlar bilan reaksiyada N-almashingan indeno-izoxinolinlar olinadi [14].

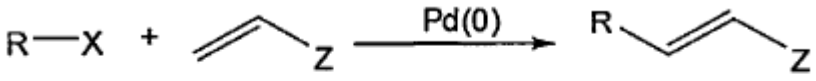


2.2.2. Arilgalogenidlardan izoxinolinlar olish usullari

Bir qancha variantlarda izoxinolin hosilalarini olish uchun arilgalogenidlar qulay boshlang‘ich birikmalar hisoblanadi.

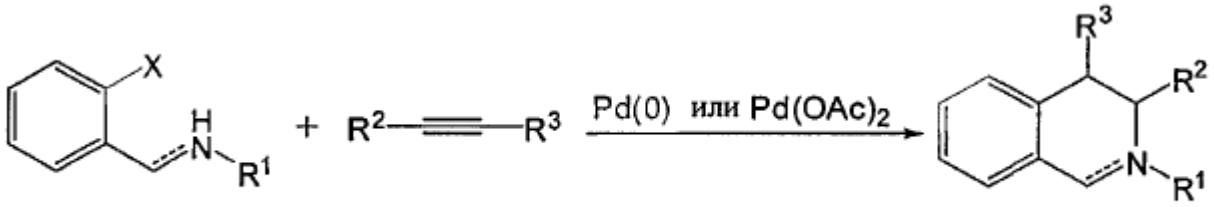
Xek reaksiyasi

Xek reaksiyasining dastlabki varianti palladiy ishtirokida olefinlarning aril yoki alkenilgalogenidlar bilan ta’sirlashuvi bilan yakunlanadi.



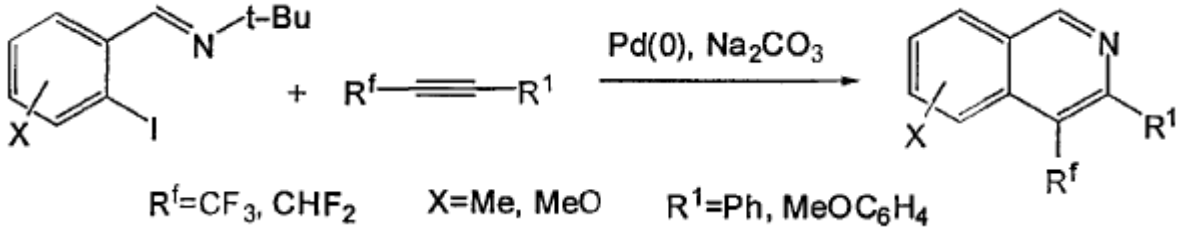
X=I,Br, OTf Z=H,R,Ar,CN,CO_2R, OR, OAc, NHAc

Xek raeaksiyasining ichki molekulyar ko‘rinishi getrosiklik birikmalar jumladan izoxinolinlar olish uchun ham qulaydir [15]. Bir qancha misollarda Xek reaksiyasining qo‘llanilishini ko‘rib chiqamiz.



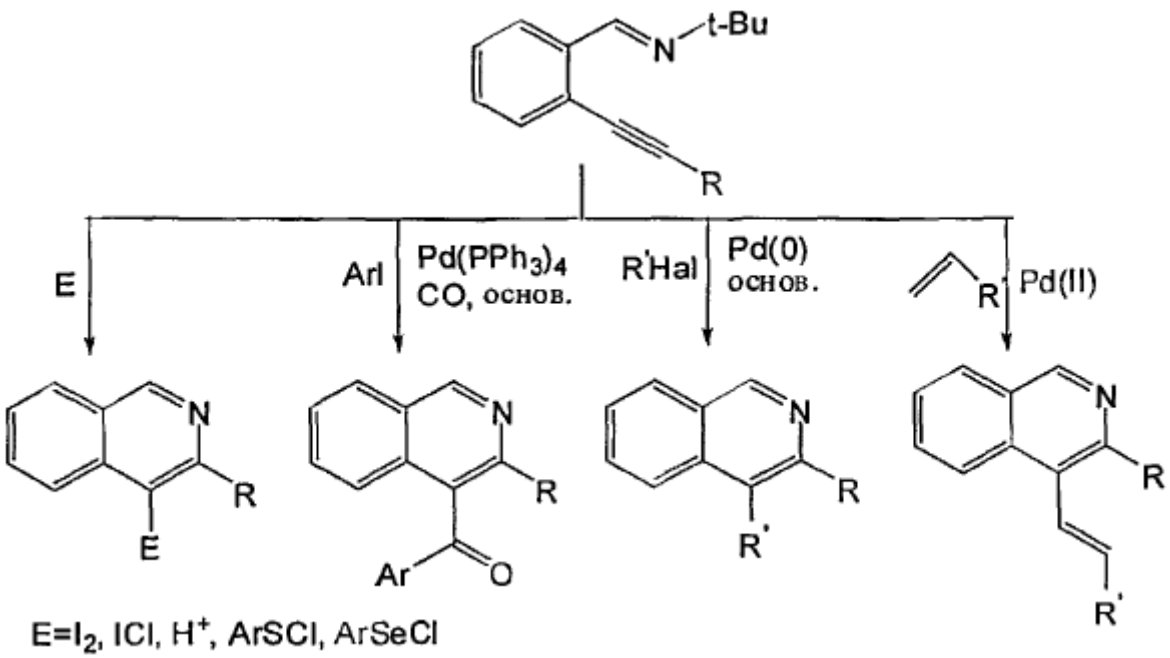
X=I, Br R^1=Ac; *t*-Bu R^2=Ph; alkyl; aryl R^3=Me, Ph, CHO, COOEt, H

Yuqori darajadagi regioseliktivlikni namoyon qiluvchi raeksiya yapon tadqiqotchilari ishida ifodalangan alkinlar bilan ta’sirlashuvidan 4-ftoralkilalmashingan izoxinolinlar olingan.

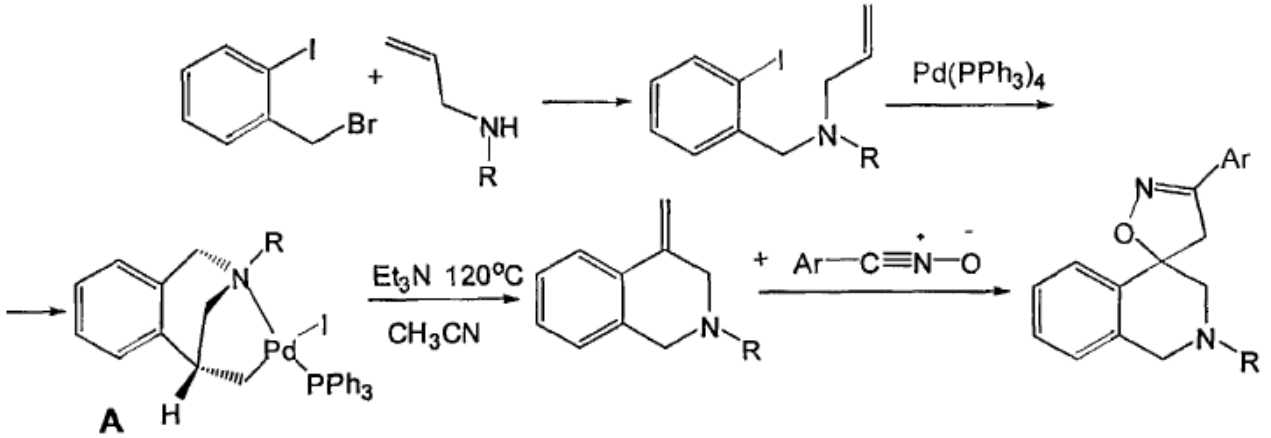


R^f=CF_3, CHF_2 X=Me, MeO R^1=Ph, $MeOC_6H_4$

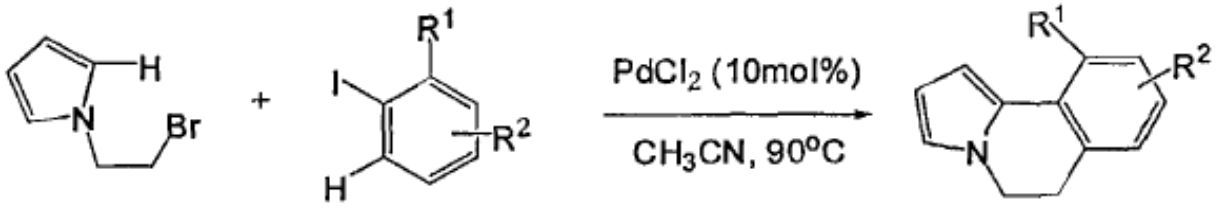
Alkinlarni iminoalkinlar bilan almashitirish reaksiyasi unumini oshirib, izoxinolin C (4) holatida o‘rinbosarlar turli-tumaligini ta’minladi [16].



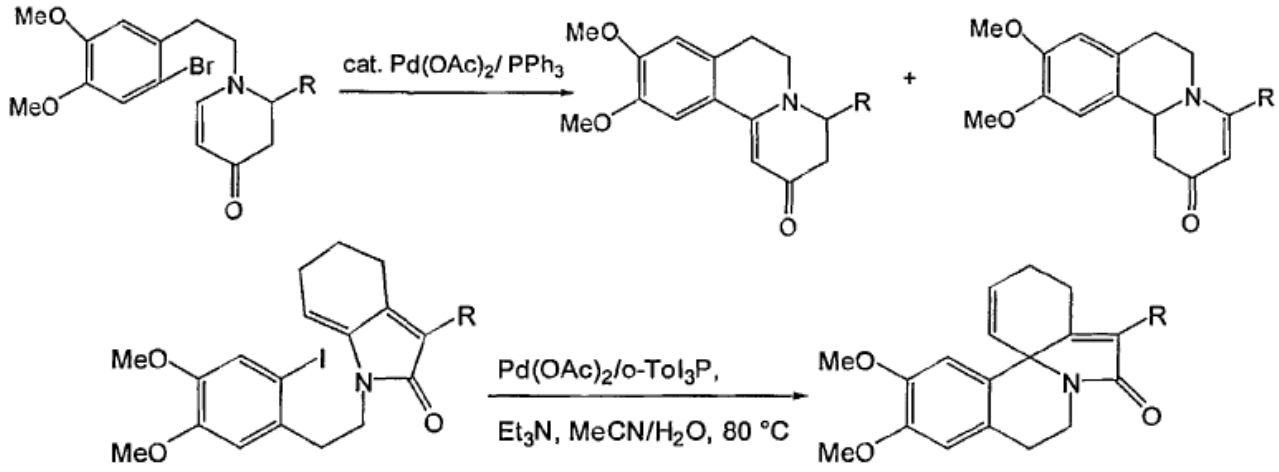
Xek reaksiyasi bo‘yicha 1,3-dipolyar siklobirikishdan oksazolin halqasi bilan 4-spirobirikkan tetrogidroizoxinolin sintez qilingan [17].



Reaksiyada barqaror α-alikil _____ yod ko‘mpleksi A hosil bo‘ladi. Maqolada molekulalararo geteroaromatik Xek raeksiyadan foydalanish bayon etilgan [18]. Bu maqola tabiiy alkaloid Krispin A va lamellarin D analoglari sinteziga bag‘ishlangan. Bu alkaloidlarda izoxinolin yadrosi arilyodidlar bilan N-bromalkilpirrol yoki pirazolning ta’sirlashuvidan olingan.

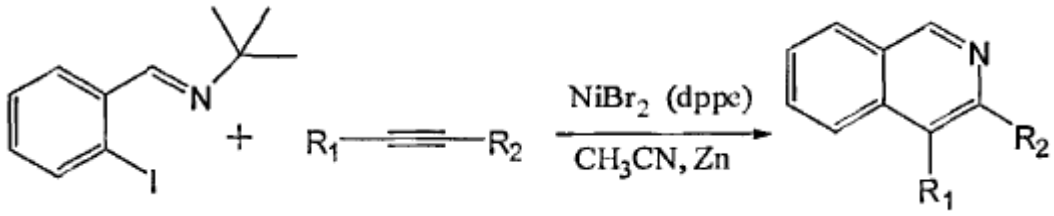


Ichki molekulyar geteroaromatik Xek reaksiyasiga misollar [19] maqolalarda keltirilgan. Boshlang‘ich arilgalogenidlar murakkablashishi bilan olinadigan izoxinolinlar tuzilishi murakkablashib, ularga bo‘lgan qiziqish ortib borgan.

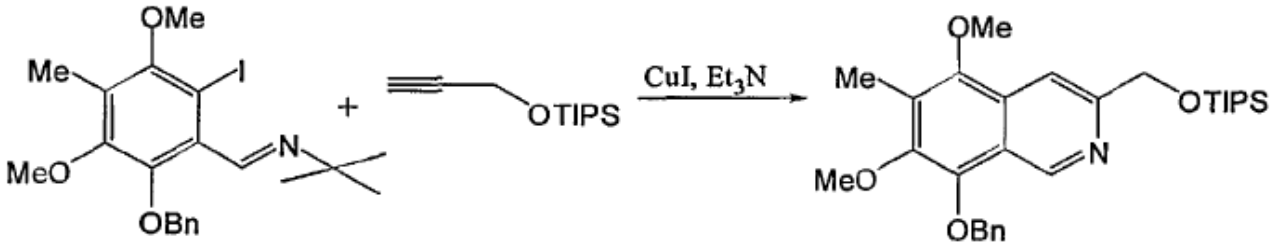


2.3. Galogenbenzoldiiminlarning alkinlar bilan turli xil palladiy katalizatorlari ishtirokida ta’sirlashuvi

Galogenbenzoldiiminning alkinlar bilan ta’sirlashuvida palladiy tuzlaridan tashqari boshqa katalizatorlarni masalan, nikel bromidni qo‘llash mumkin. Bu holatda asetilen bilan galogenbenzoldiimin reaksiyasi yuqori unumda 3,4-dialmashingan izoxinolin ajralishi bilan yakunlanadi. Jaroyonda uchlamchi- butil guruhi azot ajraladi [20].

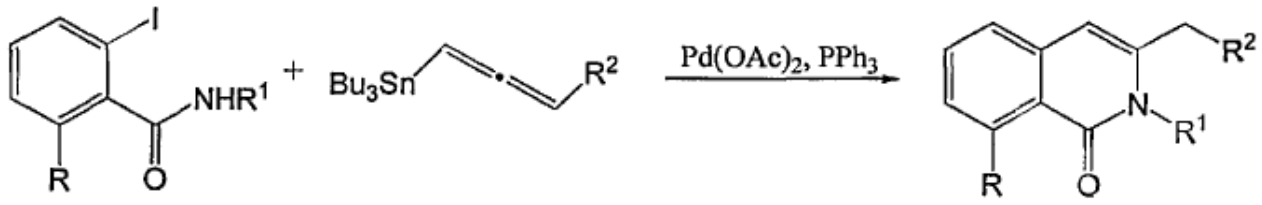


Xona temperaturasida mis katalizatori ishtirokida orto-yodimin bilan boradigan reaksiyalarda terminal alkinlardan foydalanish 3-almashingan izoxinolinlar olinishiga olib keladi.

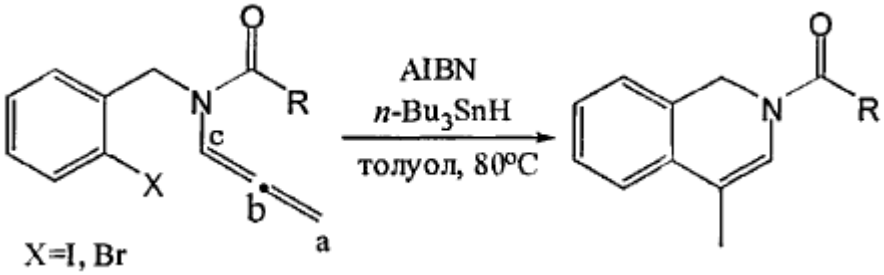


Stille krass-birikishi

Izoxinolinlar olishning yana bir qiziq usuli palladiy katalizatorlari ishtirokida organik galogenidalar bilan qalayorganik birikmalarning krass-birikishi hisoblanadi. Bu reaksiyadan foydalanib izoxinolin sintez qilishga tributilstannilallen bilan 2-yodbenzamid hosilalari ta'sirlashuvi misol bo'la oladi [21].

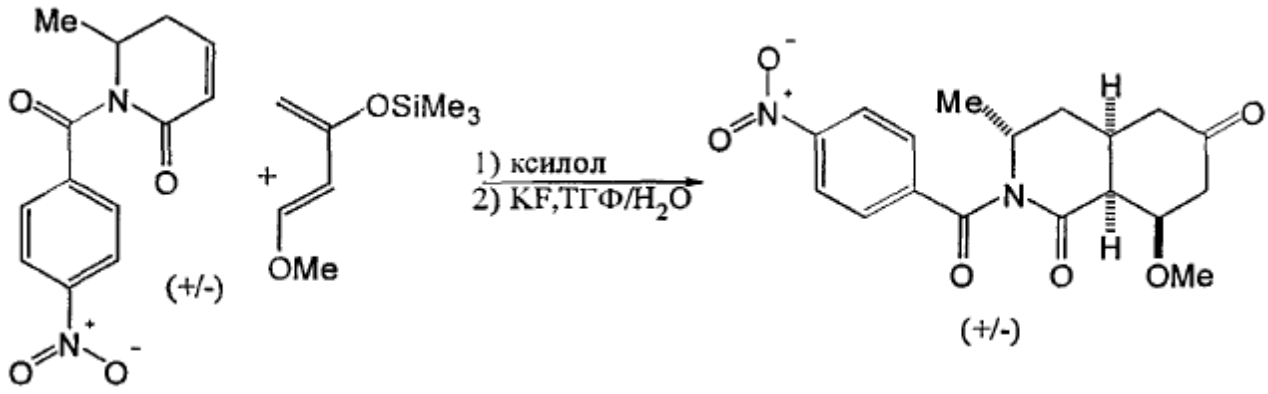


Allenaminlarning radikal sikillanishida hujum markaziy uglerod atomi bo'yicha boradi va izoxinolin hosil bo'ladi [22].

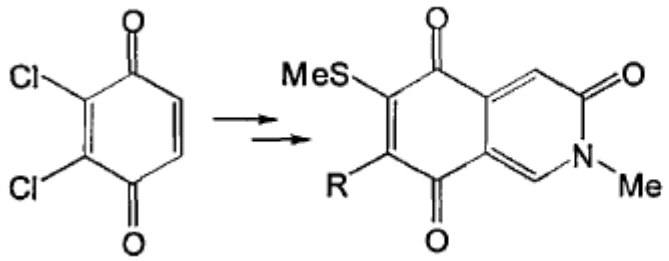


2.4. Dils-Alder reaksiyasi

Dils-Alder reaksiyasidan ko'pgina sintezlarda foydalaniladi. [23] maqolada funksionallashgan sis-gidroizoxinolin-on-lar olish uchun Danisheviskiy dieni va 6-almashingan 1-(p-nitrobenzoil)-5,6-digidropiridin-2-on ishtirokida Dils-Alder ichkimolekulyar siklobirikish reaksiyasidan foydalanilgan.



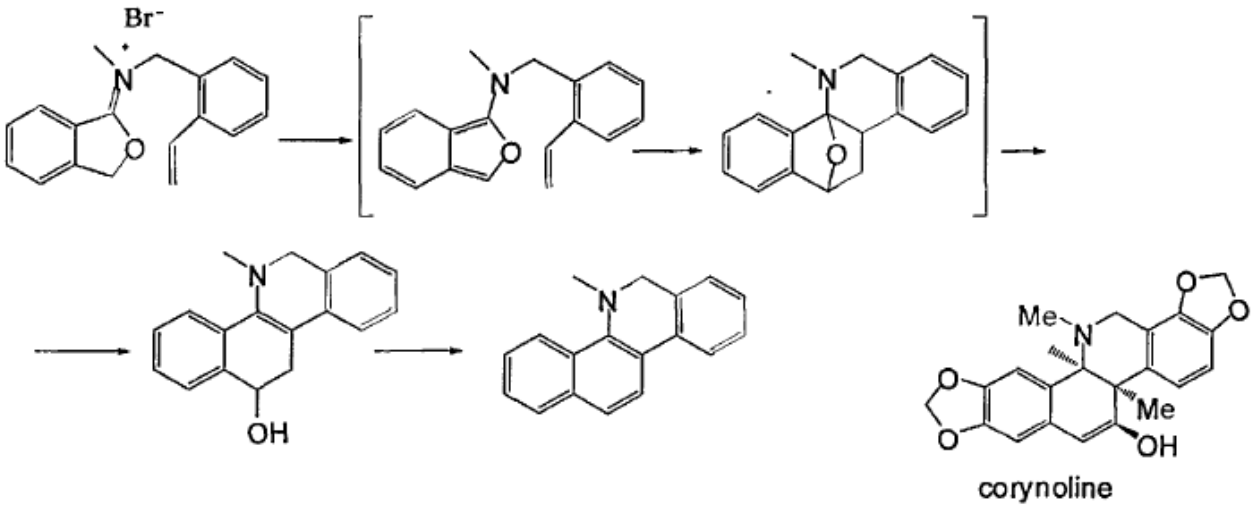
Izoxinolin qatori xinonlari – perfragelinlar A va B sintezida Dils-Alder geteroreaksiyasidan foydalanilgan (bunda 2-aza-1,3-bis(….butilgimetil-sililoksi)-1,3-butadien bilan dixlor benzoxinon ta'sirlashgan) [24].



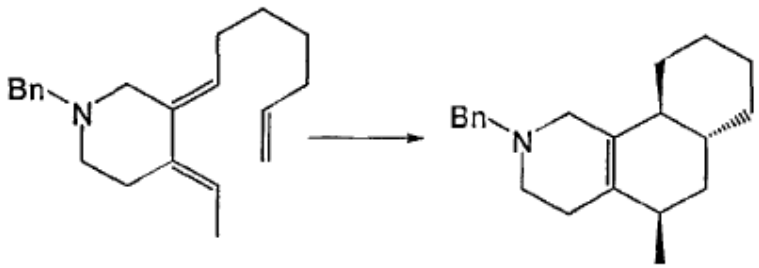
$R=NH_2$ (perfragilin A)

R=MeS (perfragilin B)

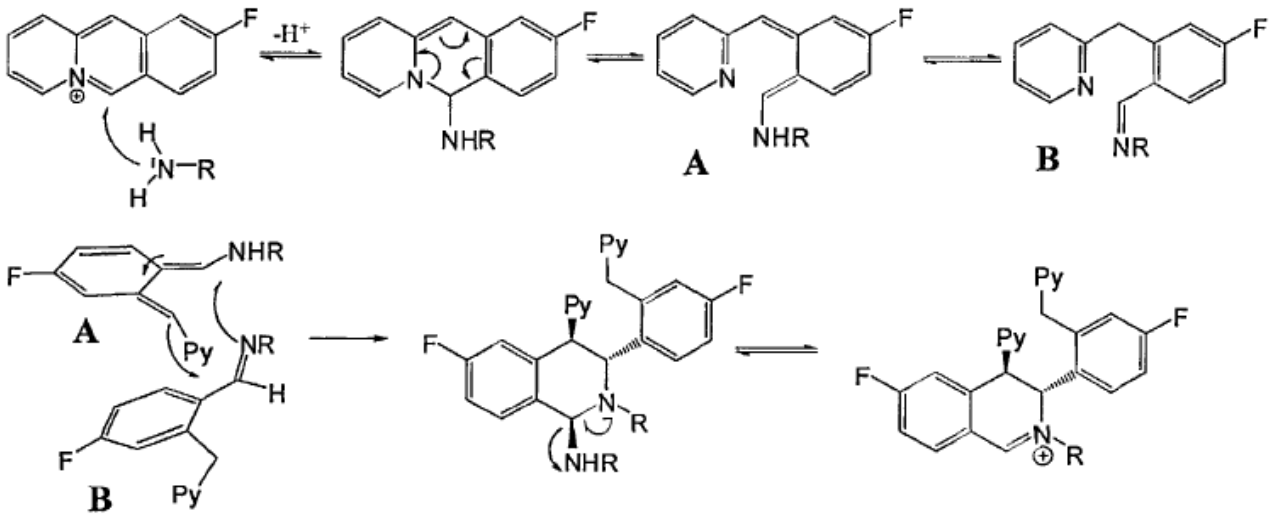
Padva [4+2]-siklobirikish ichkimolekulyar reaksiyalarida izobenzofuran aminohosilalaridan tabiiy alkaloid korinalin anologi benzo [C]-fenontridinlar sintez qilinadi [25].



(3,4….)-1-benzil-4-etiliden-3-(gept-6-eniligen)-piperidinni toluolda 7 kun davomida qizdirish ichkimolekulyar (4+2)-siklobirikishga olib keladi va trisiklik mahsulot olinadi.

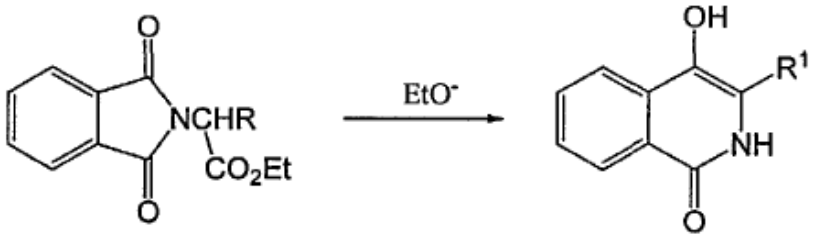


Birlamchi aminlarning 3-ftoraziridiniy ioni bilan reaksiyasida A va B birikmalar olinadi (quyida keltirilgan). Ularning Dils-Alders aza-reaksiyasiga kirishishidan yuqori diastereoseliktivlikda 6-ftorizoxinolin strukturasi hosil bo‘ladi [26].

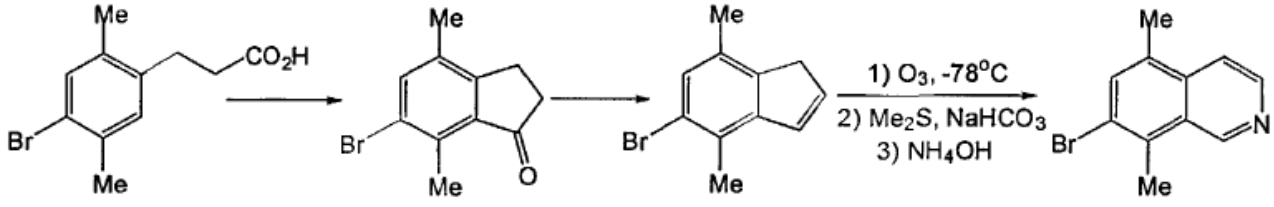


2.5. Halqaning kengayishi yoki torayishi bilan boradigan reaksiyalar

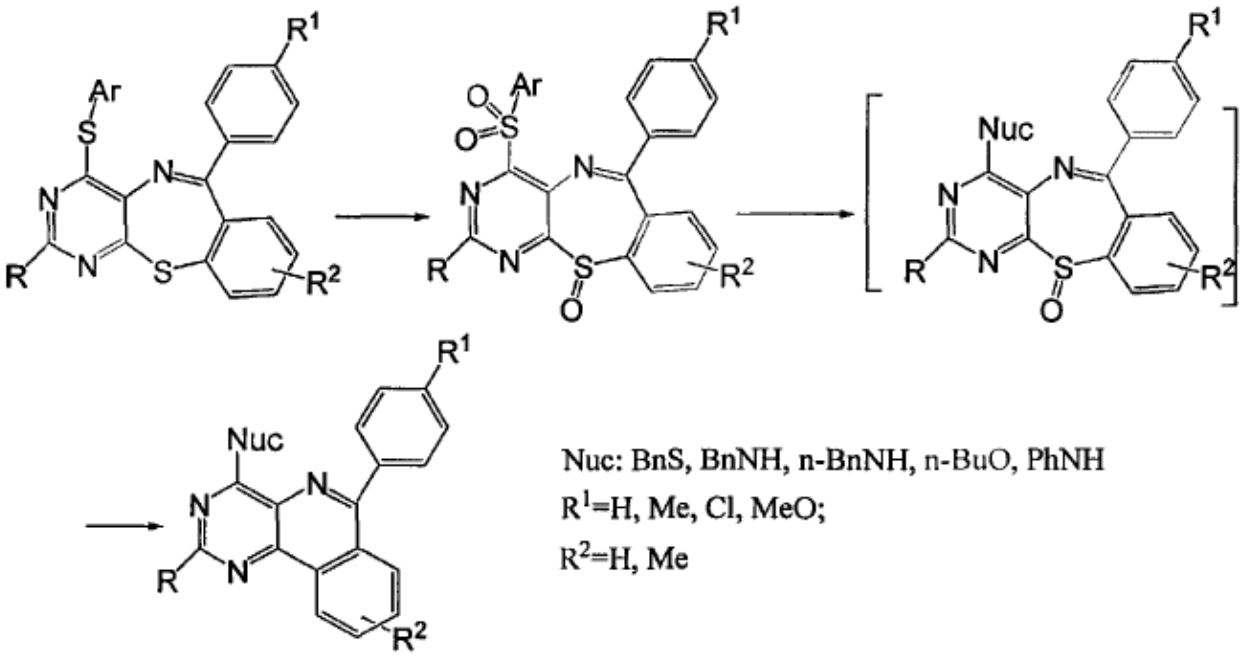
Alifatik kislota murakkab efirlari a-ftalimidohosilalari natriy etilat ta'sirida qaytaguruhlanishidan 3-almashingan 4-gidroksiizokarbostrillar hosil bo'ladi [27].



Agar R=H, R'=CO_2Et, R=Hlk yoki Ar bo'lsa karbetoksiguruh eliminiranadi (R=R') 5-Brom-4,7-dimetil-lif-inden azonlanishidan gomoftal aldegid hosil bo'ladi.Uning ammiak bilan ta'sirlashuvidan halqaning tutashishi, natijasida yuqori unumda 7-brom-5,8-dimetilizoxinolin olinadi [28].

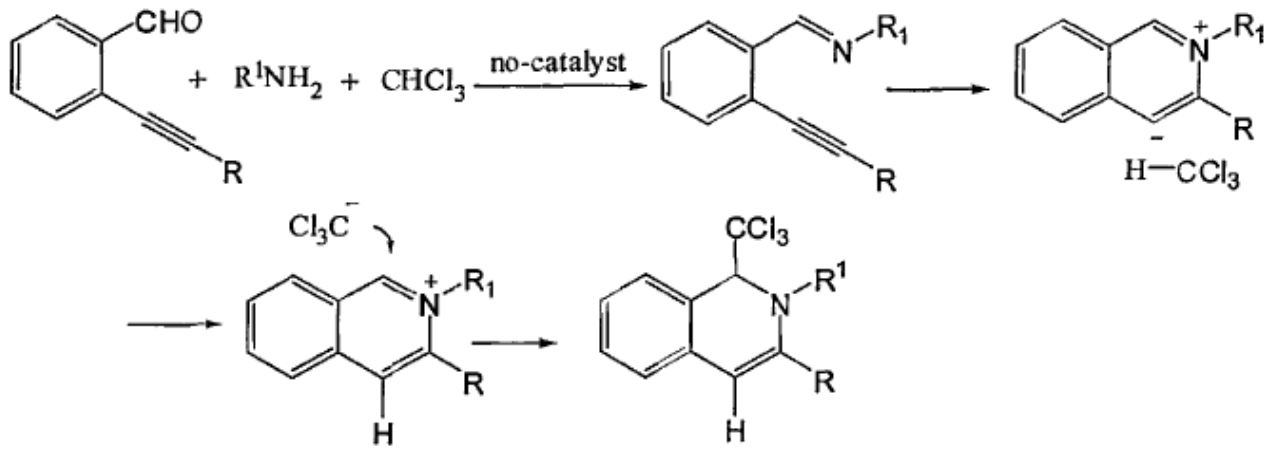


Nukleofil ta'sirida ariltiopirimido[4,5-*b*][1,4]benzotriazepin halqasidan oltingugurt oksidini ajratib, pirimidino[5,4-*c*]izoxinolinni olishda halqaning kichrayishi [29] maqolada keltirilgan.

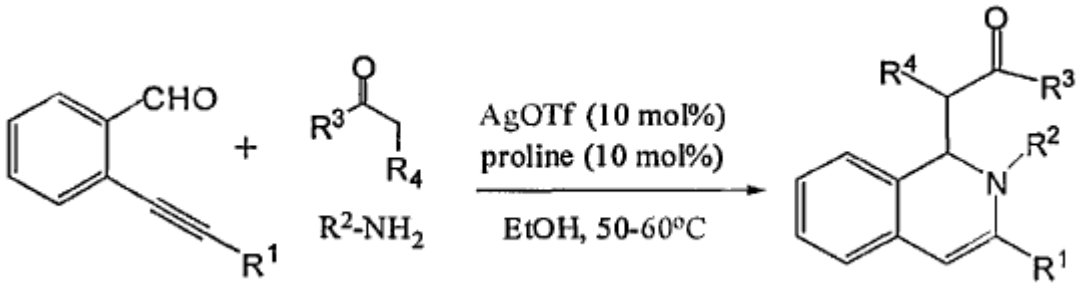


2.6. Ko‘p komponentli reaksiyalar

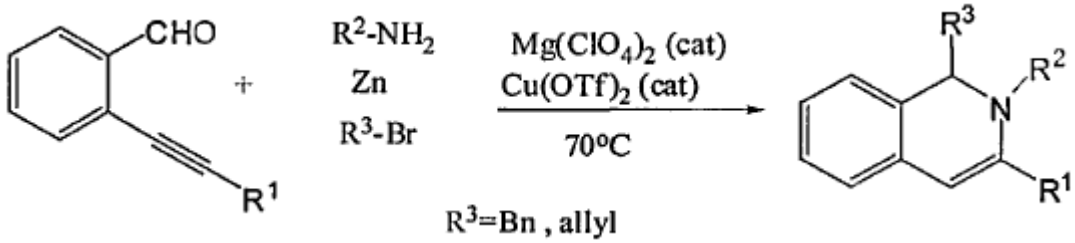
Oxirgi maxsulotni bosqichma-bosqich olish bajariladigan amallar sonini qisqartirish, shuningdekancha oddiy komponentlardan foydalanishni amalga oshirishnda ko‘p komponentli reaksiyalar juda muhimdir.Shunday usullardan biri katalizatorsizm 1,2-digidroizoxinolinlar olish bo‘lib xloroform va birlamchi aminlar bilan 2-alkinilbenzoladigidni o‘zaro ta’sirlashuvini o‘z ichiga oladi.Yapon tadqiqotchilari taklif etgan usulda xloroform pronukleofil sifatida reaksiyaga kirishadi [30]. Ushbu usul yuqori unumda N-almashingan izoxinolinlar olishda birlamchi aminlardan foydalanishga imkon beradi.



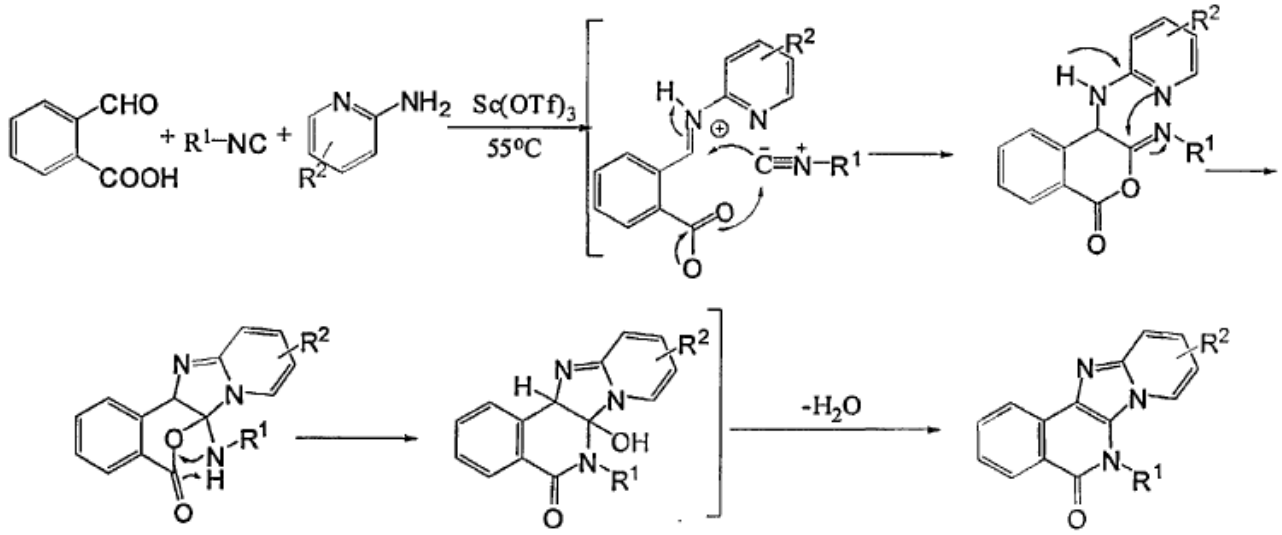
Yana bir ko‘p komponentli reaksiya amin va ketonlarni 2-alkinilbenzoldigidning o‘zaro ta’sirlashuvidan iborat bo‘lib, bunda prolin bilan Luis kislotalaridan katalizator sifatida samarali foydalanilgan [31].



Shuningdek Luis kislotalari ishtirokida 2-alkinilbenzoladigid, anilin,zux va allilbromidlarning o‘zaro reaksiyasida ham yuqori unumda {70-90 %) 1,2-digidroizoxinolinlar hosil bo‘ladi [32].

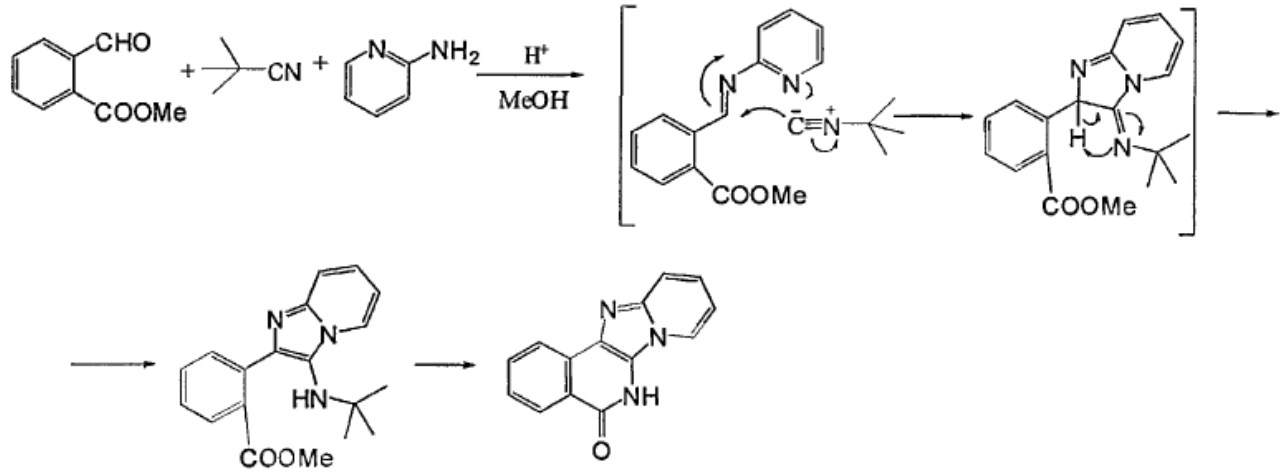


Ko‘p komponentli usulni geteroatomlini almashtirish usuli bilan birga qo‘llash keltirilgan [33]. Reaksiyada Luis kislotalari masalan, $Sc(OTf)_3$ dan foydalanish izoxinolinlar hosil bo‘lishunumining pasayishiga olib keladi.

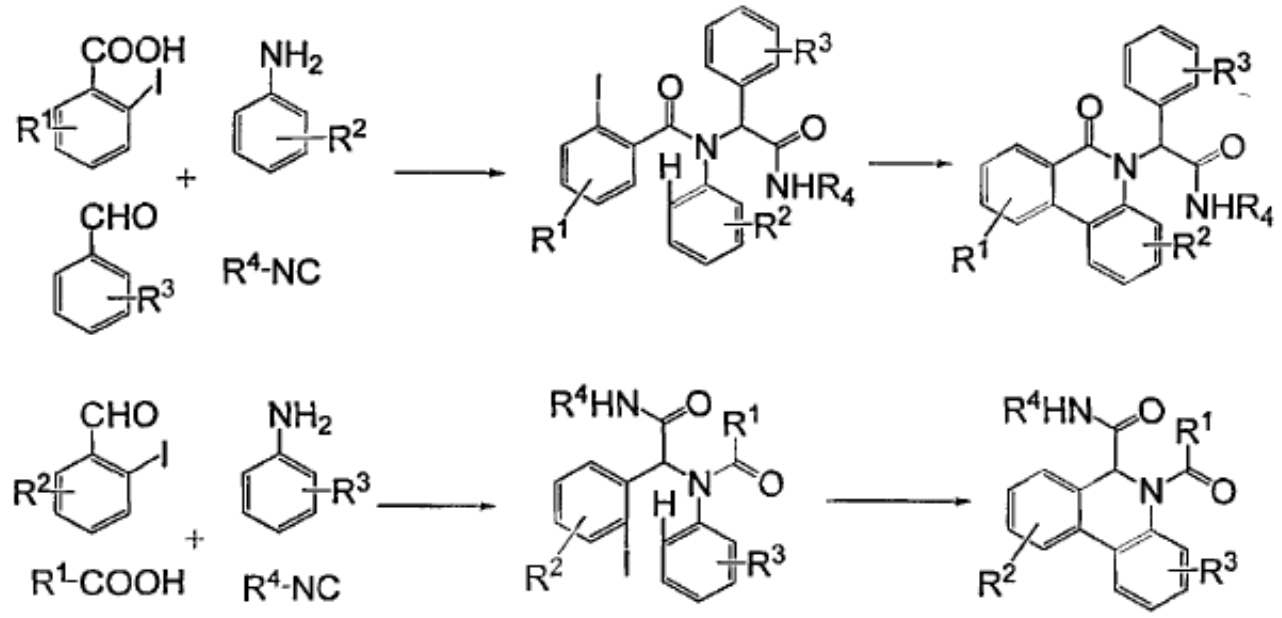


Ishda yuqoridagi usulning ancha to‘ldirilgan varienti keltirilgan. Bunda 2-aminopiridin, kaliy sianid va formilbenzoy kislotalarni uchkomponentli ta’sirlashuvidan pirido[2,1:2,3] midazo [4,5-C] izoxinolin-5(6 H)-on,

alkilgalogenidlar bilan reaksiyadan esa O-va N-alkillangan hosilalar aralashmasi olinadi. Ishda 2-formilbenzoy kislota metil efiri va 2-izosiano-2-metilpropanlardan foydalanilgan, hamda birikma hosil bo‘lishining boshqa mexanizmi taklif etilgan oraliq maxsulot hosil bo‘lmaydi [34].

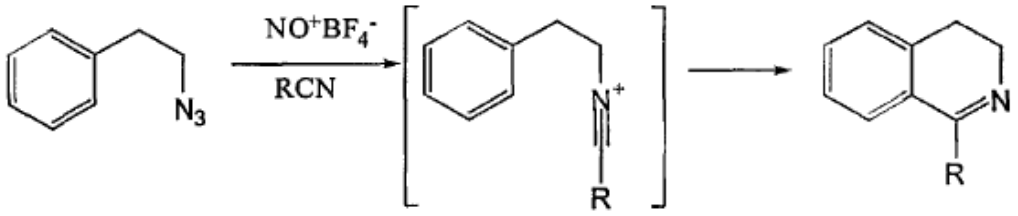


To‘rt komponentli Ugi reaksiyasi (U-4 CR) da palladiy katalizatorli ichki molekulyar Xek reaksiyasidan foydalanib 2- bosqichda izoxinolin olinadi. Alifatik amin,aldegid, karbon kislota va izosianitlar ta’sirlashuvidan a-asilaminoamid olinadi. a-asilaminoamid katalitik sistema ($Pd(OAc)_2$) PCy_3 va N-metildisiklogeksi (amin) ishtirokida yuqori unum bilan izoxinolinga aylanadi. Aromatik amindan foydalanilgan holatda esa fenantridinli struktura olinadi [35].

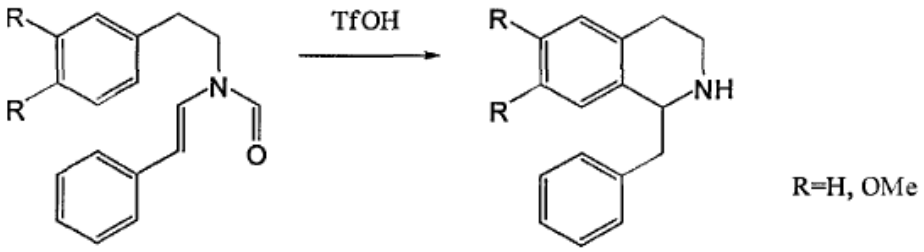


Usullarga keying kiritilgan o‘gartirishlar taklif etilgan yo‘nalishlarni tubdan o‘zgartirmasada e’tiborga molik hisoblanadi. Masalan fenitilazid, nitrozoniy ioni

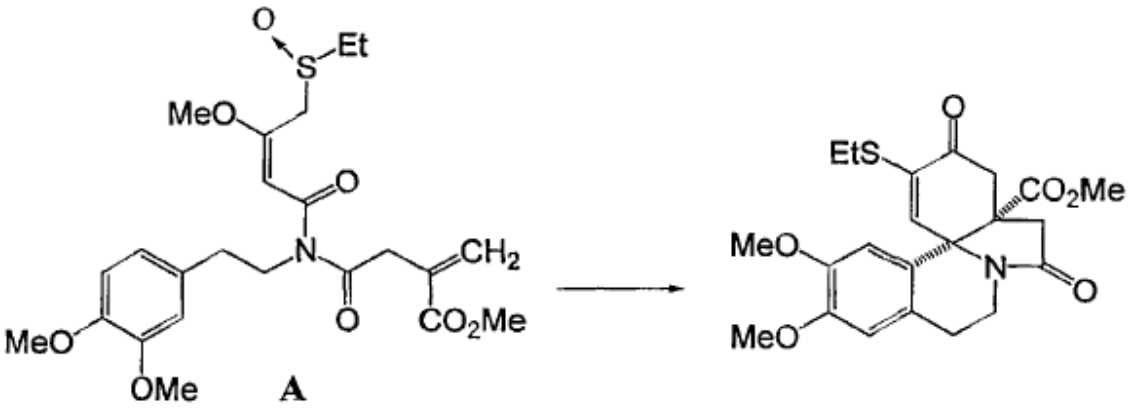
ishtirokida nitrozoniy bilan Ritter reaksiyasiga o‘xshash reaksiyaga kirishib [36], 1-R-almashingan 3,4-digidroizoxinolinlar hosil qiladi



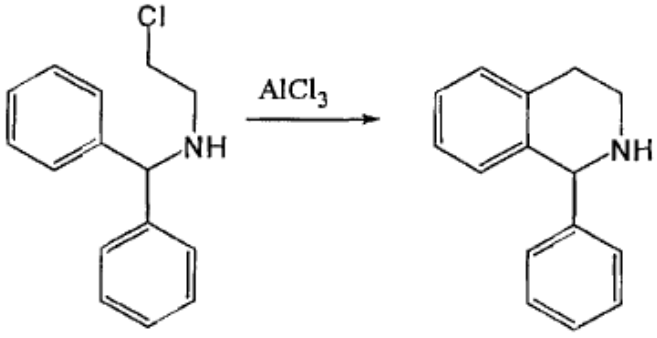
Brensted yoki Luis kislotalari ta’sirida N-stirilformamidlardan 1,2,3,4-tetrogidroizoxinolinlar olish mumkin [37].



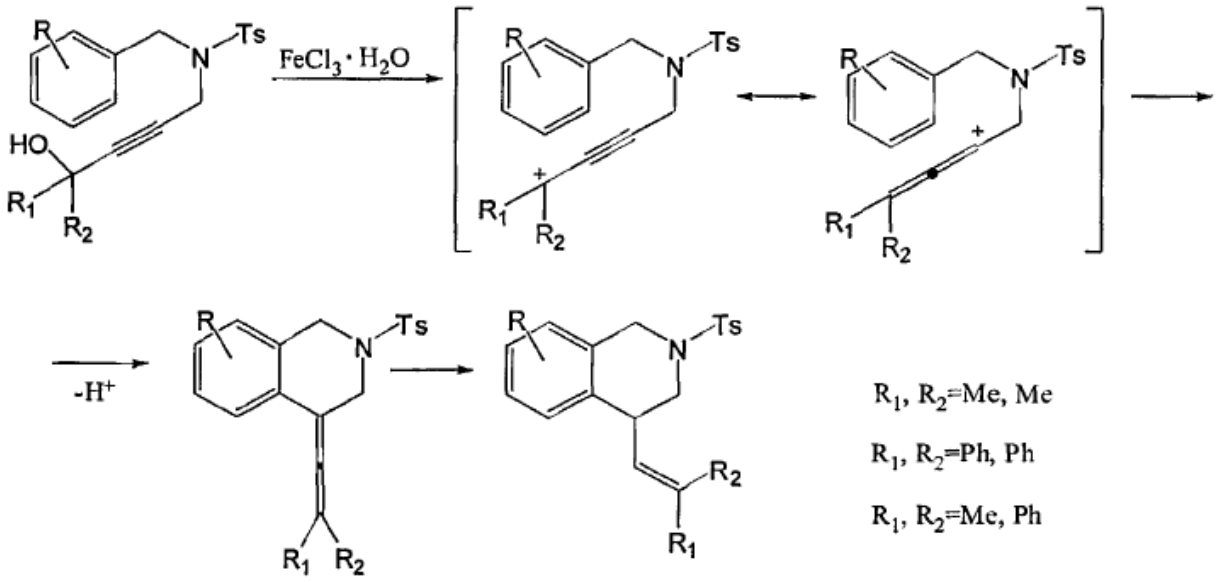
Pummerer reaksiyasi ham e’tibordan chetda qolmagan [38] ishda A-ioni bog‘langan Mannix-Pummerer reaksiyasidan foydalanib izoxinolin molekulasini yig‘ishning istiqbolli imkoniyatlari bayon etilgan.



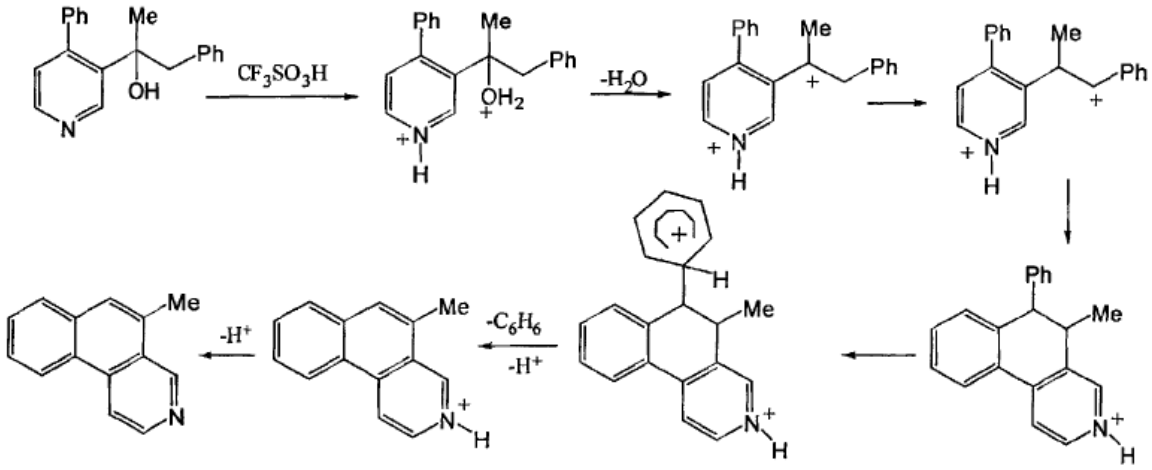
Fridel-Kraft bo‘yicha ichki molekulyar alkillash usuli ham diqqatga sazovor [39].



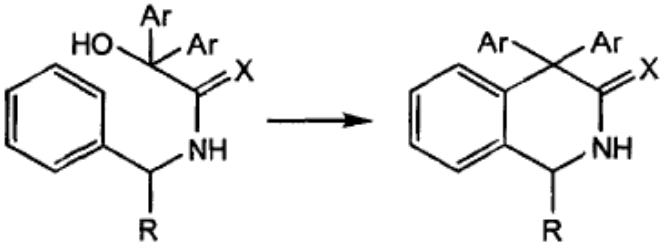
[40] maqolada N-tozilillangan benzinamino almashingan propargil spirtidan foydalanib Fridel-Krafts reaksiyasi bo‘yicha izoxinolin olishga misol keltirilgan.



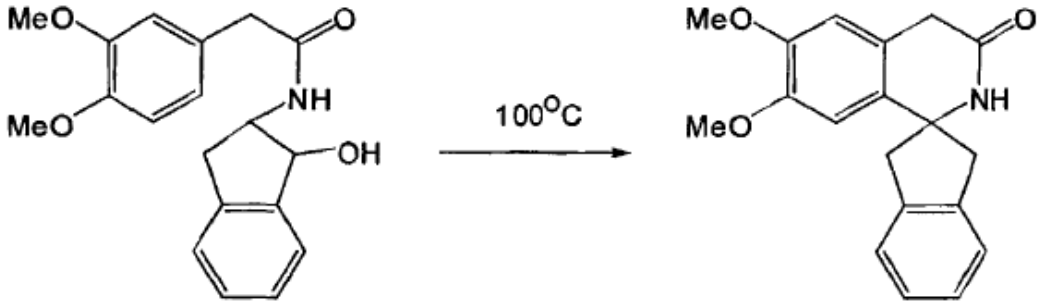
[41] maqolada piridin saqlagan birikmalardan triftormetansulfon kislotalar ta’sirida izoxinolin olish bayon etilgan. Taklif etilgan reaksiya mexanizmi quyidagicha: piridinli halqasining protonlanishi va gidroksil guruhlar chiqib ketishi natijasida 1,4-dikation hosil bo‘ladi. Maxsulot unumi 93 % ni tashkil etadi.



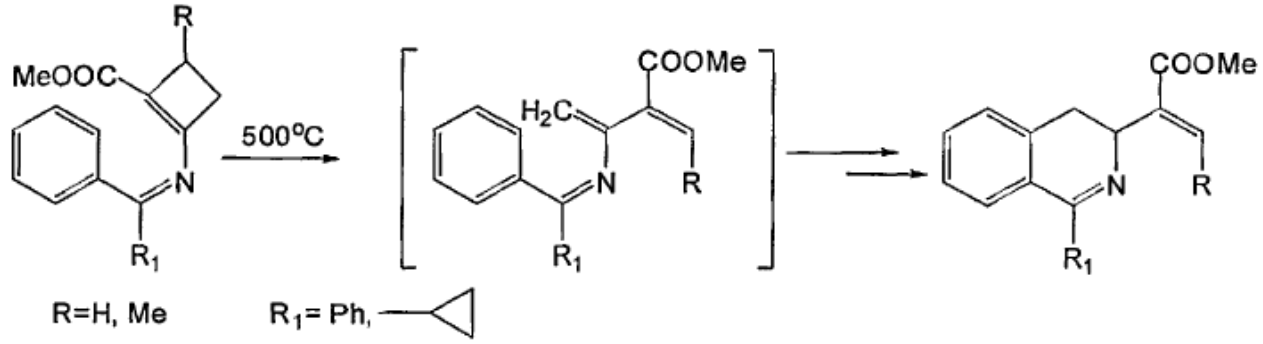
1,4-almashingan izoxinolinlarni diarilglikol kislota benzilamidlari va ularning dezoksohosilalaridan olish mumkin [42].



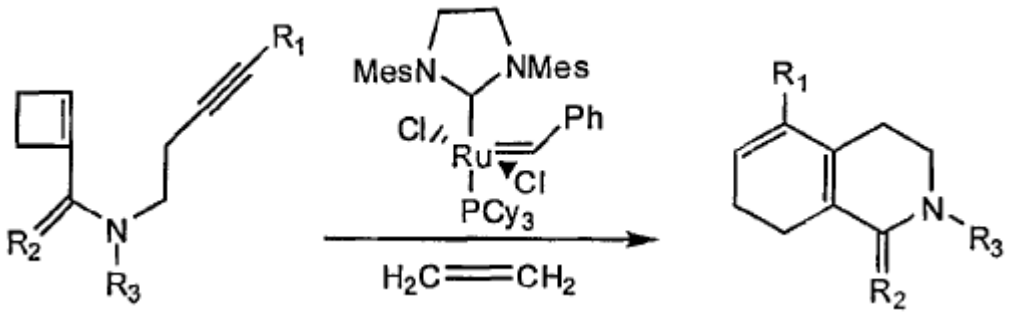
Amidokarbinolning polifosfat kislotalar ta’sirida sikllanishidan spiroizoxinolin-3-on sintez qilingan [43].



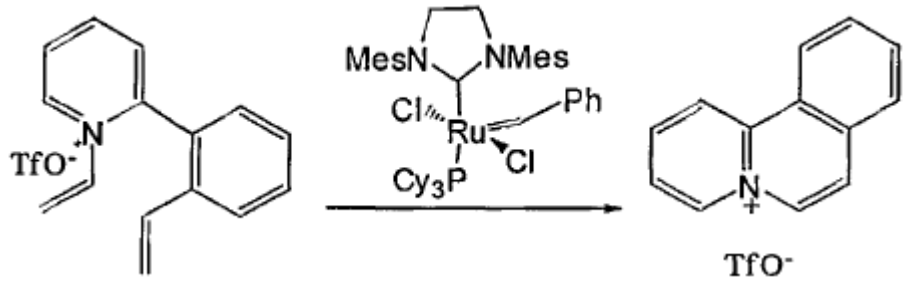
3,4-digidroizoxinolinil-2-akril kislota metil efiri imulsion vakuumli piroliz yordamida olingan.



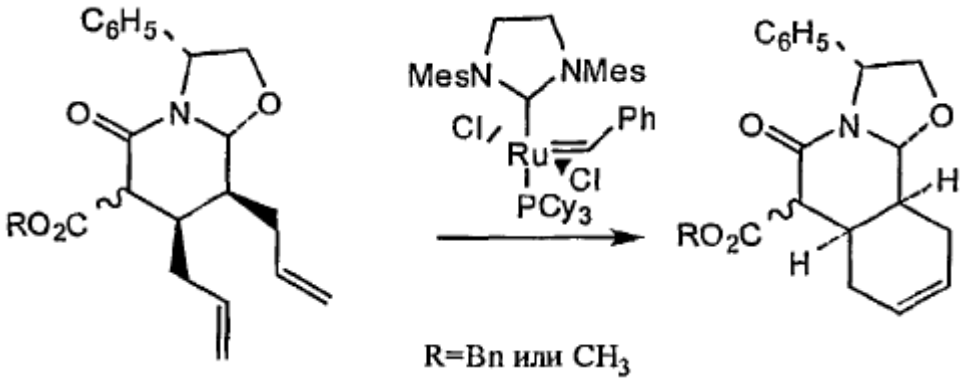
5,6 va 7-a’zoli geterosikllar sintezining umumiy usullari olefinlarning Grabbs metotezisiga asoslangan. Mualliflar [44] maqolada izoxinolin yadrosi sintezi uchun ushbu usuldan foydalanishgan. Bu ishda izoxinolin olish uchun siklobutinilamindan foydalanishga misol keltirilgan. Reaksiyada oraliq rutiniy-karboniy kompleksi hosil bo‘lad, kompleksning buzilishidan olti a’zoli halqa olinadi. Ushbu holatda 1,2,3,4,7,8-geksagidroizoxinolin aromatic halqasi 5-holatiga o‘rinbosar ham kiritish mumkin.



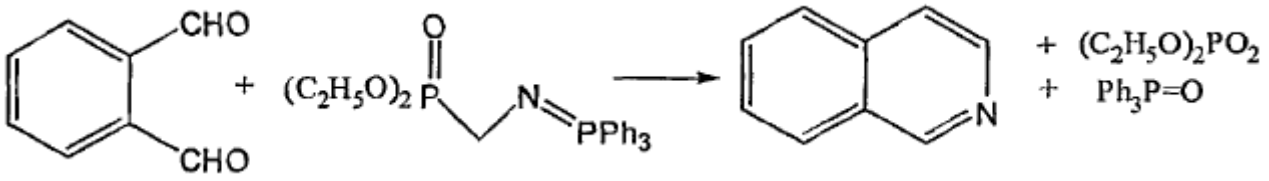
Ushbu usuldan foydalanishga yana bir misol ishda keltirilgan .Mahsulot unumi 83% ni tashkil etadi.



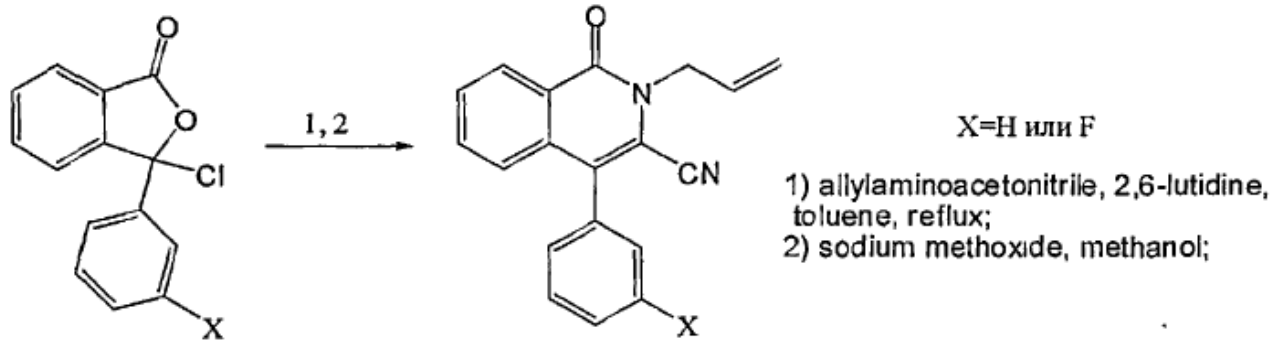
Grabus katalizatoridan (5% mol) foydalanib ,karbosiklik halqaning tutashishi hisobiga yaxshi unum bilan (85 %) izoxinolinli mumkin [45].



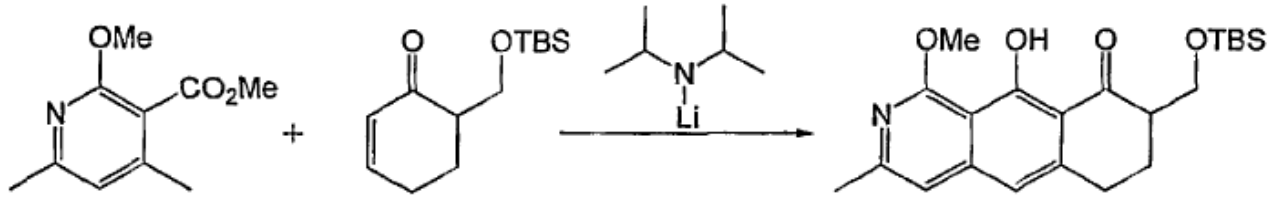
Izoxinolinlar sintezining 1,2-monoazobisilidlar qo‘llanilishi bilan bog‘liq yana bir usulni ko‘rib chiqaylik .Bu usul ftal aldegidi ishtirokidagi Vittig va Vittig azo-reaksiyalarini o‘z ichiga olgan [46]. Izoxinolin unumi 55% ni tashkil etadi .



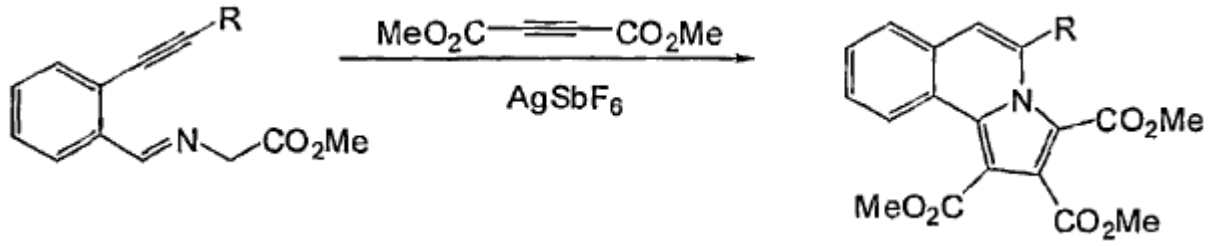
3-fenil 3-xlorizobenzofuranonning allilaminoasetonitril bilan reaksiyasi amid hosilasini beradi. Uni natriy metaksid bilan qayta ishlab 3-sionoizoxinolin-on olinadi [46]



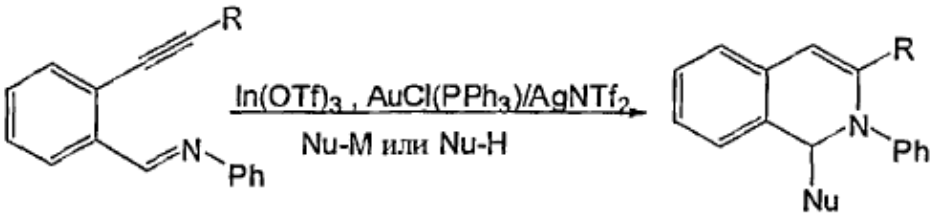
Izoxinolinlar sintezi uchun 2-metoksi-4,6-dimetilpiridin-3-korboksilatning almashingan siklogeksan va litiy diizopropilamid bilan Klayzui kondensatsiyasi tipidagi 1,4-birikishidan ham foydalanish mumkin [47].



Alkenil [-]M-benzilidenglisinatning dimetilasetilen dikarboksilat bilan kumush birikmalari ishtirokida tasirlashuvi 3-manoalmashingan 1,2-digidroizoxinolin hosilalari olinishi bilan boradi . Bunday usul pirrolizoxinolin olish uchun ham qo‘llanilgan . Bu birikma lanellarin sintezida oraliq mahsulot hisoblanadi [48]



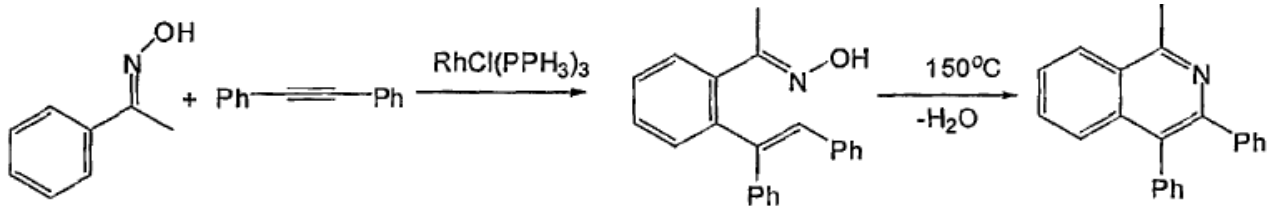
Shu tadqiqotchilar 2-(1-alkinil) anilaldimin nukleofil birikishi so‘ngra sikllanish orqali 1-holatda o‘rinbosar bo‘lgan izoxinolinlarni sintezlashgan Reaksiyada katalizator sifatida Luis kislotalaridan foydalanilgan.



Nu= CH_2NO_2, $CH(CN)_2$, $CH(CO_2Me)_2$, CCPh

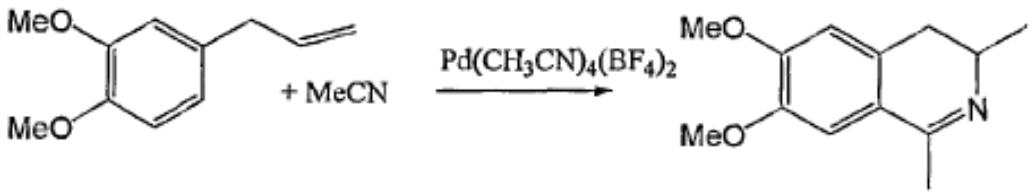
R= Ph, CH_2OBn

Alkinlarning radiyli katalizatorlar ishtirokida asetofenon oksimlari bilan ta’sirlashuvidan 90% unumi bilan 1,3,4-trialmashingan izoxinolin olingan.

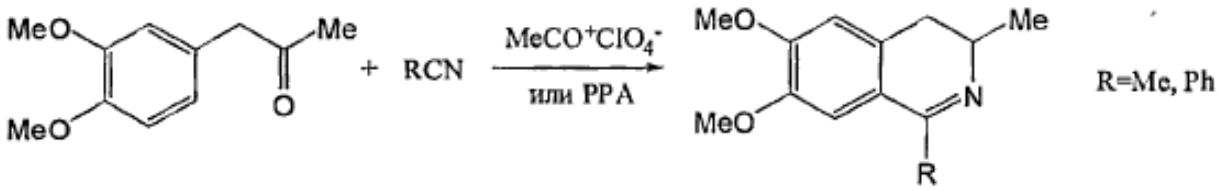


2.7. Ritter reaksiyasi

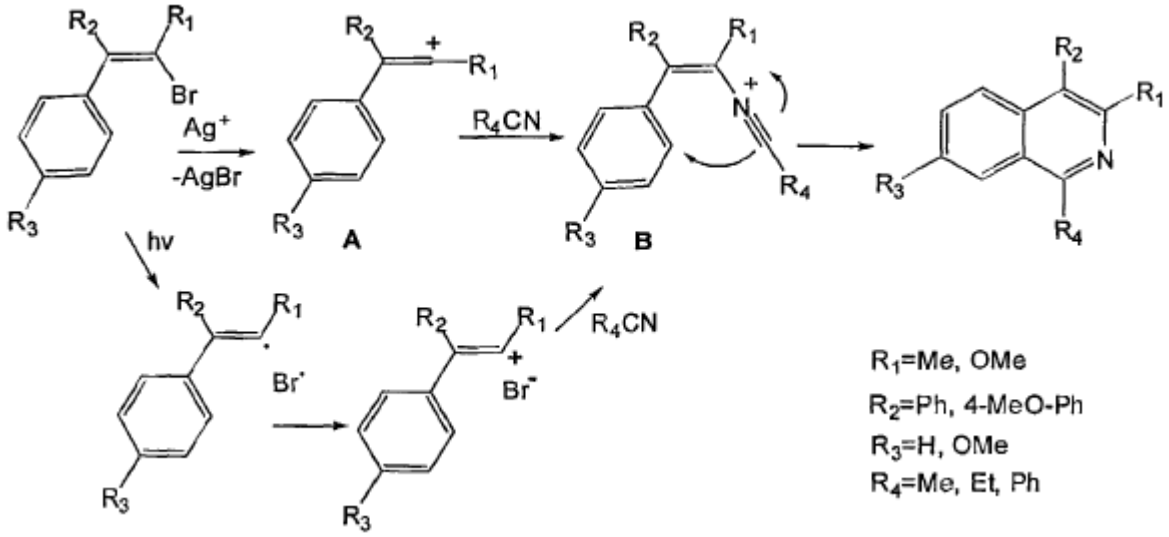
Bu reaksiyaning dastlabki variantida alifatik nitrillar,aromatik va getrosiklik kislotalar bilan olefinlar va konsentrlangan sulfat kislotadagi spirtlarning o‘zaro ta’siri N-alkilalmashingan karbon kislota amidlari hosil bo‘lishiga olib keladi. Bu reaksiya molekulaga azot atomini kiritish hamda C-N bog‘ini hosil qilishning qulay usuli hisoblanad. So‘ngi vaqtlarda ushbu usul turli getrosikillar, jumladan izoxinolinlar olish uchun foydalanilmoqda. Reaksiyani amalga oshirish uchun ko‘pgina konsentrlangan sulfat kislota qo‘llaniladi. Shuningdek polifosfat, triftorsirka va perxlorat kislotalardan ham foydalaniladi. Luis kislotalari ham qo‘llanilgan [49] ishida yuqori elektrofil $Pd(CH_3CN)_4(BF_4)_2$ kompleksi ta’sirida asetonitril va alkilbenzoldan izoxinolinlar sinteziga misollar keltirilgan.



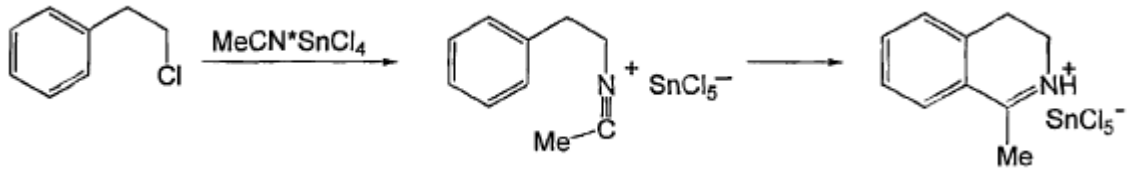
Adabiyatlar taxlili shuni ko‘satadiki, Ritter reaksiyasi asosida hosilalari sinteziga bag‘ishlangan ishlar yetarlicha o‘tkazilgan. Olinish usullari bir-biridan karbkationning hosil bo‘lishi bilan farq qiladi [50] maqolada 3,4-dimetoksifenilaseton va aseto-yoki polifosfat kislota yoki sirka kislotasi eritmasidagi benzonitrillardan 6,7-dimetoksiizoxinolinlar sintezi bayon etilgan. Avval karbonil guruh uglerod atomi faollashtirilgan, keyin nitril nukleofil hujumi sodir bo‘lgan.



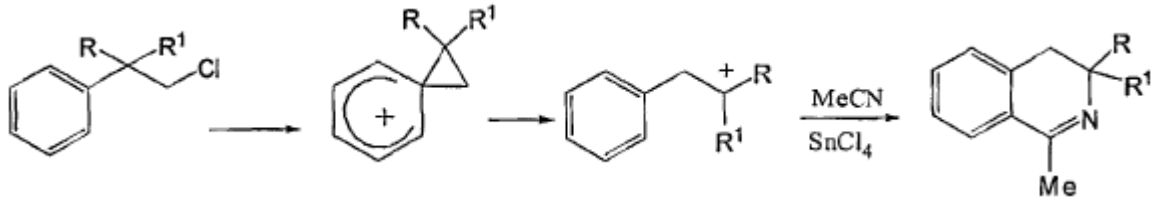
[51] ishida 3-arilvinilbromidlarning nitrillar bilan ta’sirlashuvidan 1,3,4-almashingan izoxinolinlar hosil bo‘lishi keltirilgan.



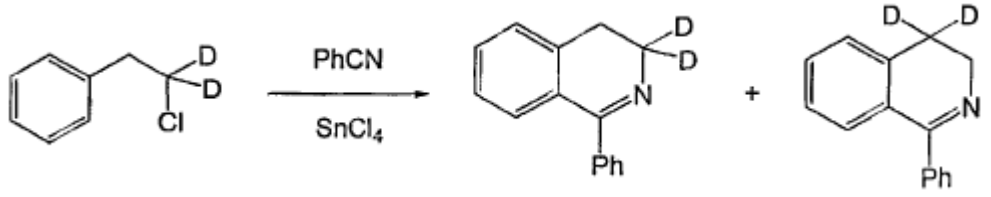
P-arilvinil kationi nurlanish yoki kumush ioni ta’sirida hosil bo‘ladi. Mualliflar maqolada $SnCl_4$ ishtirokida sianidlar bilan 1-xlor-2-feniletan reaksiyasida N-(2-fenetil) nitriliy kationi hosil bo‘lishi va uning izoxinolingacha sikllanishini taklif etishgan.



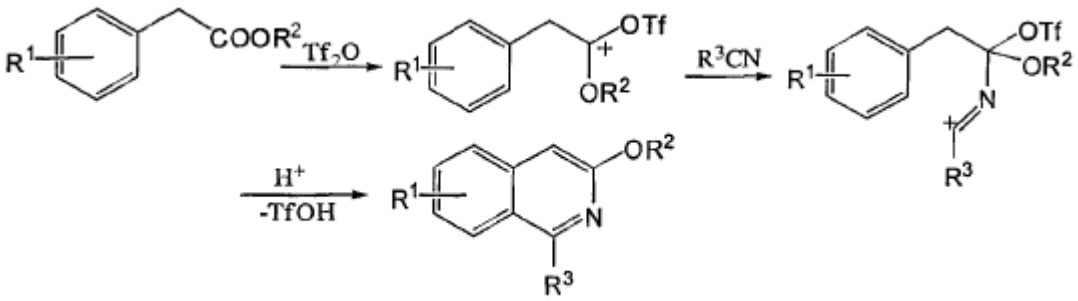
Ancha keyingi [52] ishda to‘liqroq mexanizm keltirilgan. P-mono va P-dialmashingan feniletilxloridlarning nitrillar bilan $SnCl_4$ ishtirokidagi reaksiyasidan 3,4-digidroizoxinolinlar hosil bo‘lishi taklif etilgan. Reaksiyada oraliq maxsulot fenoniy ioni hosil bo‘ladi.



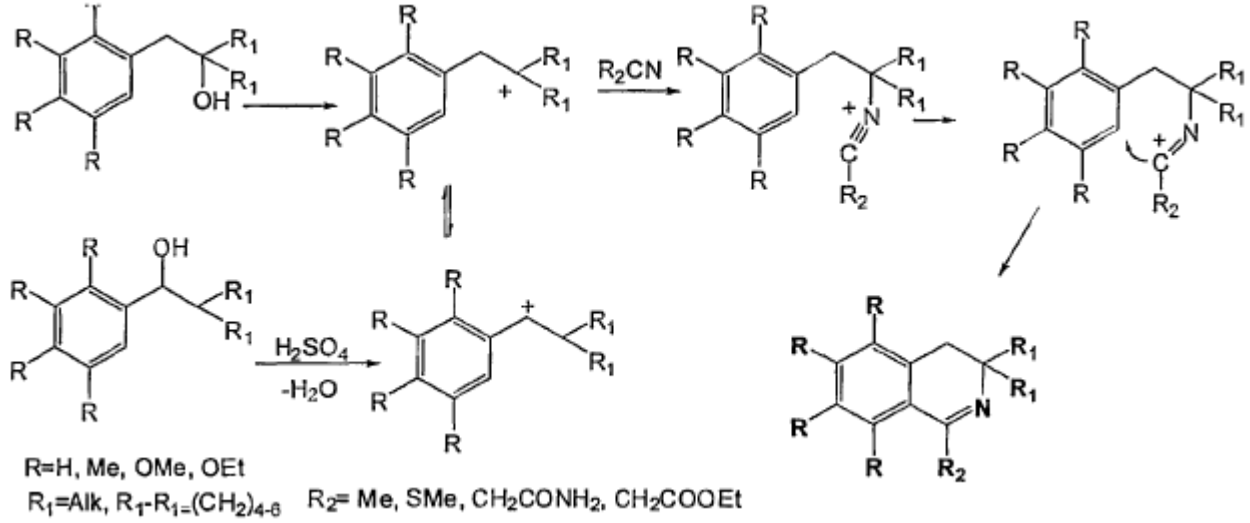
Deyterirlangan α-dialmashingan fenetilxloriddan 2 yo‘nalishda halqaning bir xil ochilishi natijasida 1:1 nisbatda 3- va 4-dialmashingan mahsulotlar aralashmasi hosil bo‘lishi shunday xulosa qilishga imkon beradi.



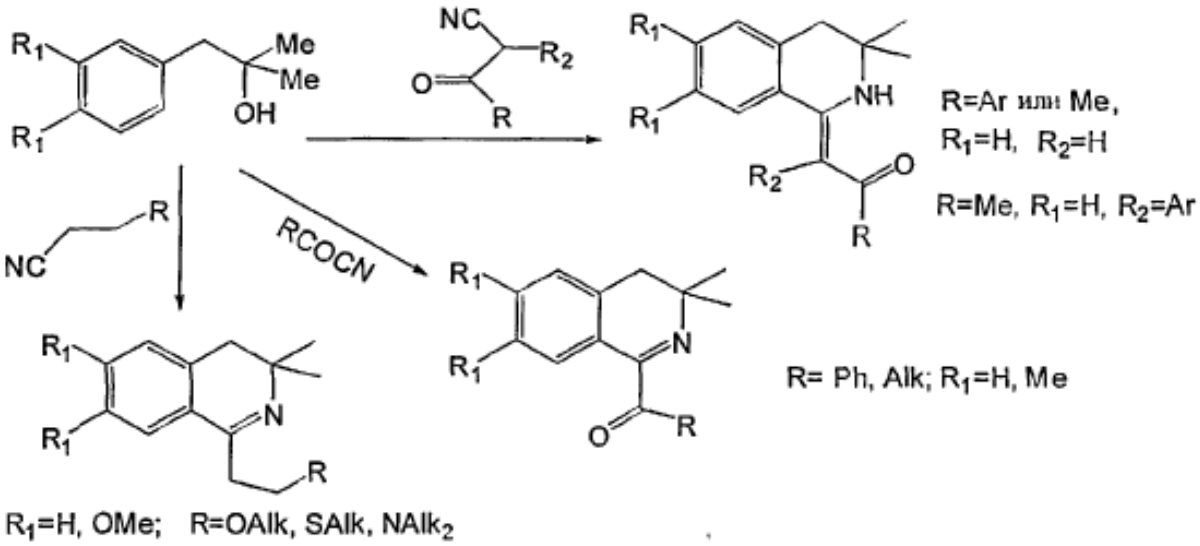
3-galogenetilbenzollardan 1-getarilizoxinolinlar olish imkoniyati ham mavjud. [53] maqolada murakkab efirli gurulardan karbkation hosil bo‘lishiga misollar keltirilgan.Bunda getrosikllanish nitriliy ioni hosil bo‘lishi bosqichi orqali boradi:



Ritter reaksiyasi asosida 3,4-digidroizoxinolinlar hosilalari sinteziga yana bir yondoshuv [54] ishlarda ko‘rib o‘tilgan.Dialkilbenzilkarbinollar va 2-fenil-1-fenilpropan-1-ollarning nitrillar bilan ta’sirlashuvi ham nitriliy ioni hosil bo‘lishi bosqichi orqali boradi.

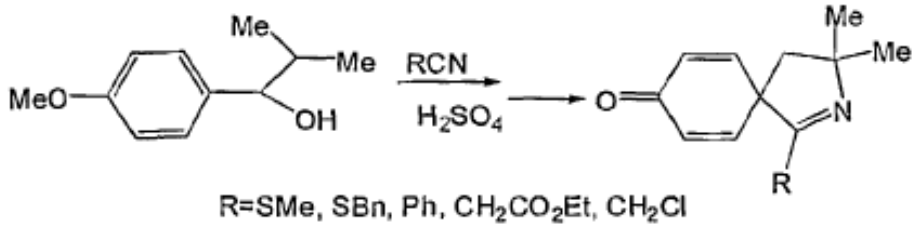


Bu usulni benzo-3,4-digidroizoxinolinlar va geksogidrofenantridinlar sintezi uchun ham qo‘llash mumkin [55]. Ritter reaksiyasining ushbu modifikatsiyasida nitrilli komponent sifatida OH-,SH-,NH-, saqlagan birikmalarni sianetillashdan olingan asilasetonitrillar, asilnitrillar galogenasetonitrillar va nitrillardan foydalanish mumkin.

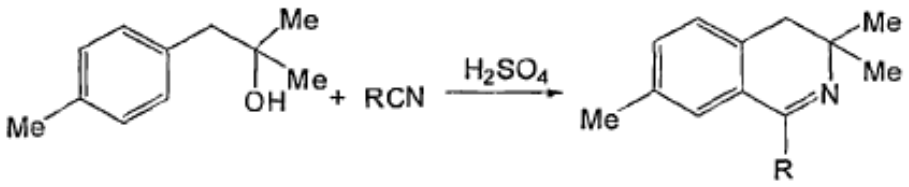


Dialkilbenzilkarbinollarning sianid kislota bilan reasksiyasidan ham C(1) halat bo‘yicha almashingan 3,3-dialkildigidroizoxinolinlar olish mumkin.Ritter reaksiyasi bo‘yicha 3,4-digidroizoxinolin hosilalari sintezi usulida karbinollar orqali universal nomlash mumkin emas. Chunki, u bir qancha cheklanishga ega.

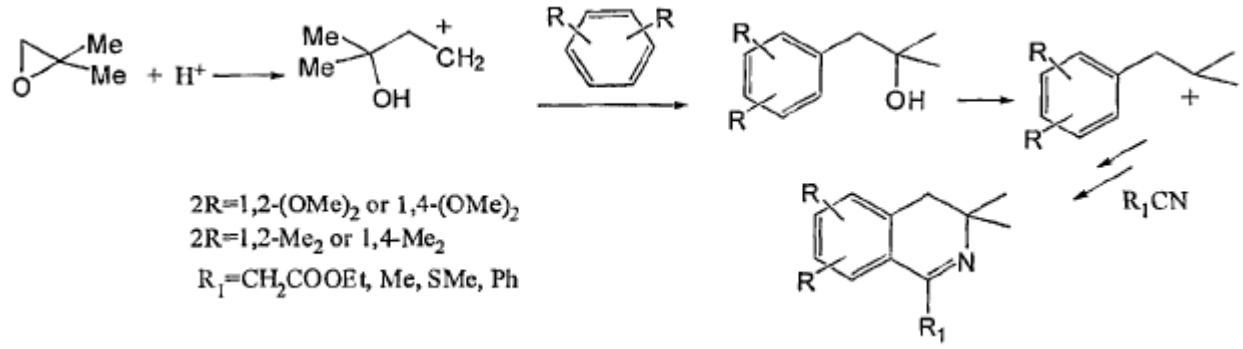
Bunday sikllanishni nitril guruhi guruhi bilan birga kuchli elektronoakseptor guruhlar saqlagan (trigalogenasetonitrillar, sionamidlar) nitrillar bilan amalga oshirib bo‘lmaydi.Dietilaminoasetonitrillar bilan reaksiya bormaydi. Bundan tashqari, geterosikllanish reaksiyasining o‘tishiga,olinadigan birikmalar turiga ham ta’sir ko‘rsatadi. Karbinol aromatik halqasidagi o‘rinbosar tabiati va holatiga ham ta’sir etadi [56] ishda 2-metil-4-metoksifenilpropan-1-ol ishtirokidagi Ritter reaksiyasida 3,4-digidroizoxinolin hosilasi bilan birga almashingan 3,3-dimetil-2-azaspiro [4,5] deka-1,6,9-trien-8-onlar ham hosil bo‘lishi keltirilgan.



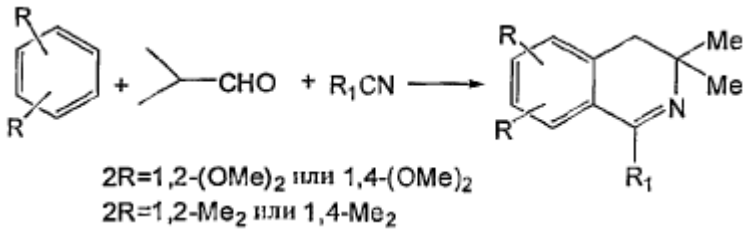
4-holatda bitta metil guruhi bo‘lgan dialkilbenzilkarbinollarning nitrillar bilan ta’sirida 3,4-digidroizoxinolin hosilasi hosil bo‘ladi.



Karbinollar orqali 3,4-digidroizoxinolin hosilalarini olishning alternativ usuli sifatida avvalgi magniyorganik sintez bilan olishning yana bir qulay va oddiy foydalanish usuli ishlab chiqilgan. Usul almashingan aren izobutilen oksidi va konsentrlangan sulfat kislotadagi nitrillarning uch komponentli kondensatsiyasiga asoslangan [57].

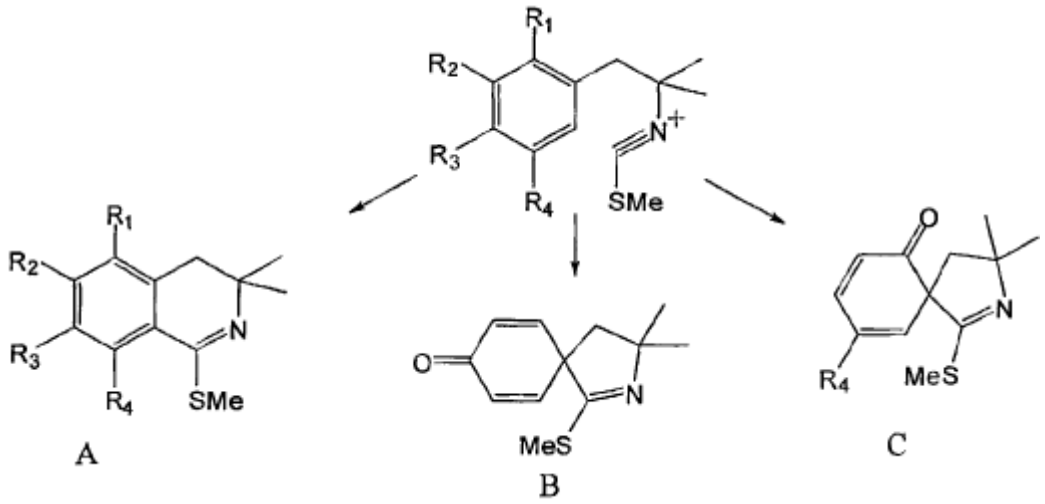


Usulning yaqqol ustun tomoni oddiylik va maxsulotlar yuqori unumi hisoblanadi.Lekin, usulning ko‘satilgan qiymati zaharlilik va izobutilen oksid, qimmatliligi kabi jihatlar pasaytirmoqda. α-tarmoqlangan aldegidlar aynan izomoy aldegiddan foydalanish ham kamchiliklarni yuzaga keltirmoqda.1,2-(yoki 1,4-)-dimetoksibenzollar hamda orto-va para-ksilollar bilan izomoy aldegid va nitrillarning uch komponentli ta’sirlashuvidan mos ravishda oson 3,4-digidroizoxinolinlar hosil bo‘ladi.

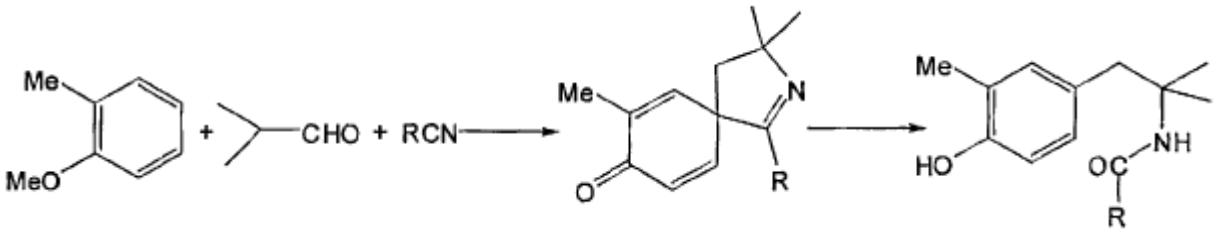


Ritter reaksiyasi sharoitda uch komponentli ta’sirlashuv aromatik halqadagi o‘rinbosar holati va tabiatiga bog‘liq bo‘lib, 3,4-digidroizoxinolin hosilalari yoki spiranli tizimlar hosil bo‘ladi.Reaksiya yo‘nalishiga ta’sir etuvchi asosiy omil aren orto-va ipso uglerot atomlari zaryadlar qiymati hisoblanadi. Ipso-holatga nisbatan

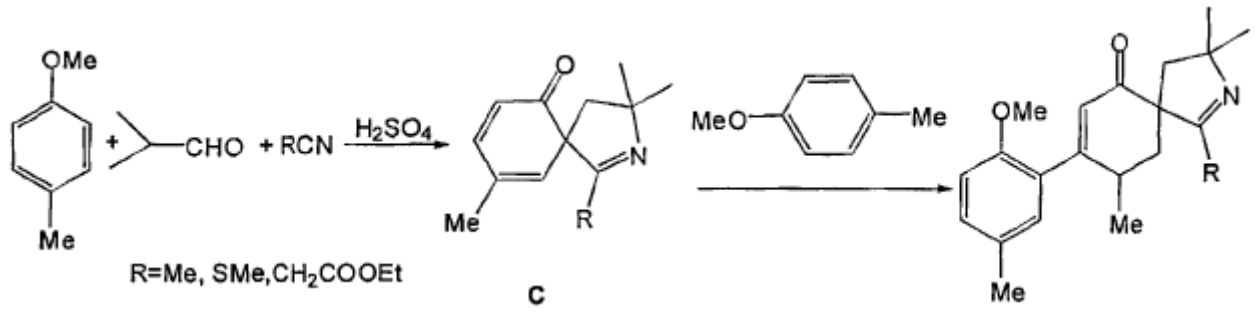
orto-atomda zaryad katta bo‘lib, faqat 3,4-digidroizoxinolin A hosilasi hosil bo‘ladi. Qarama-qarshi holatda spirosikllanish amalga oshadi. Masalan anizol,α-va -metoksinaftalinlardan foydalanilganda spirogetrosikllanish mahsuloti olinadi [58]



Bundan tashqari faqat oltingugurt saqlagan spiranlar B olish mumkin (anizol holatida). Boshqa nitrillar komponentlar ($NCCH_2CO_2Et$, PhCN,BnCN,$NCCH_2Cl$) dan foydalnilganda dienon-fenol qayta guruhlanish amalga oshadi va fenilamidlarga muofiq spiro B birikmalar hosil bo‘ladi. Shunday o‘zgarishlar 2-metilazinol,izomoy aldegid va qator nitrillar reaksiyasida ham kuzatiladi.

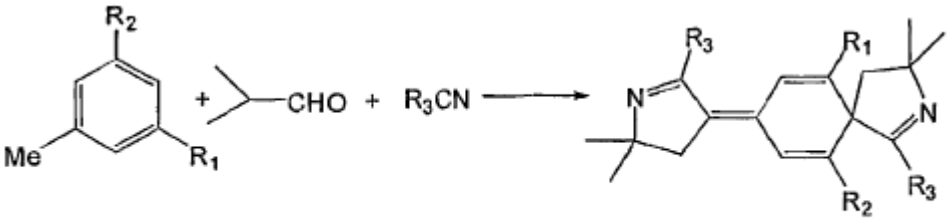


Spirobirikma C ga yana bir aren molekulasining qo‘shilishidan noodatiy maxsulot olingan [59].



n-galogenalmashingan alkoksiarenlardan emas P-metilanizoldan foydalanilganda ham shunga o‘xshash maxsulot olingan. Ko‘pchilik hollarda

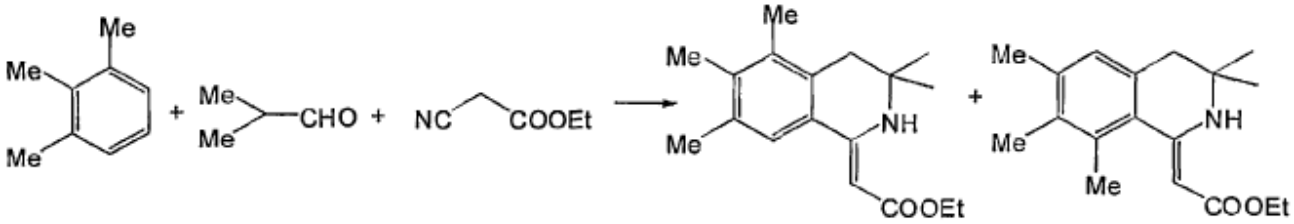
arendagi zaryadi katta o‘rinbosar sterik qiyinchiliklar tug‘dirib, hujum yo‘nalishiga ta’sir ko‘rsatadi. 2 ekvivalent izomoy aldegid, 2 ekvivalent nitril va bir-biriga nisbatan meta-holatda joylashgan metil va metoksiguruhli arenlarning 3 komponentli reaksiyasida noodatiy maxsulot olingan [60]. 3,4-digidroizoxinolin hosilasi bilan birga kaskodli gidrosikllanish maxsuloti ham ajratib olingan.



R_1,R_2=H, Me(a), Me,Me(b), Me, OMe(c), H, OMe(d)

R_3=Me, SMe,CH_2COOEt

2-metil-1-(2,3,4-trifenilmetil)propan-1-oldan foydalanilganda ham shunga o‘xshash natijaga erishilgan.1,2,3- va trimetilbenzollardan foydalanilgan holatda 3,4-digidroizoxinolin hosilasi hosil bo‘ladi.

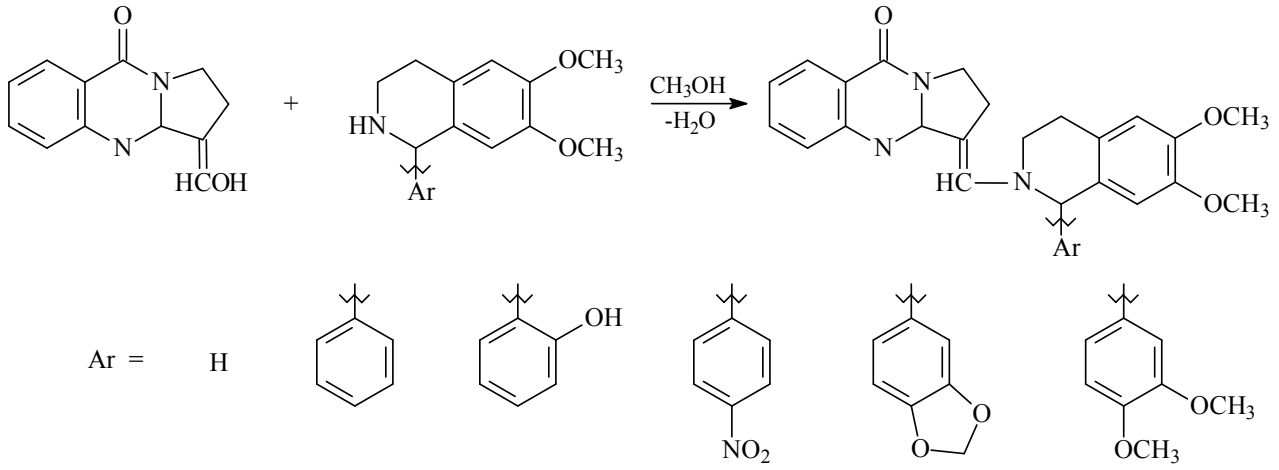


[61] ishda Ritter reaksiyasi sharoitida 1-benzil-3,4-digidroizoxinolin hosilalarini olish keng o‘rganilgan. Adabiyotlar tahlili asosida shuni xulosa qilish mumkunki, izoxinolin yadrosi turli-tuman usullari bo‘lib, bu usullar juda muhimligini anglatadi. Lekin, 3-holatda gem-dimetil guruh tutgan 3,4-digidroizoxinolinlar hosilalari olinishiga Ritter reaksiyasi uch komponentli variantlardan foydalanib karbinollar orqali izoxinolinlar sinteziga misollar deyarli keltirilmagan. Ammo, bunday usullar karbinol va arenlar o‘rinbosarlari holati va tabiatiga juda sezgir bo‘lib, oldin o‘rganilmagan o‘rinbosarli karbinollar va arenl;ardan fydalanilganda keyingi reaksiya yo‘nalishi o‘rganish talab etiladi.

2.8. Xinozolin-izoxinolin alkaloidlari sintezi

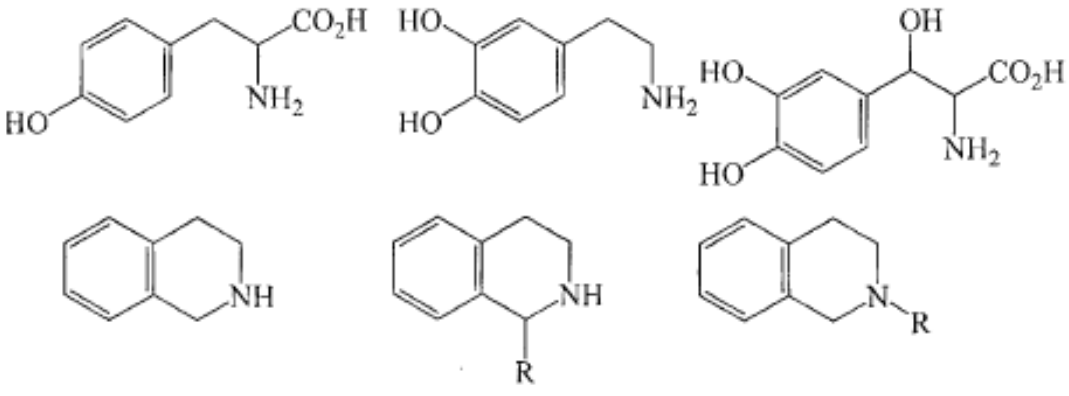
[62] maqolada α-oksimetiliden-2,3-trimetilen-3,4-digidroizoxinolin-4-onning 6,7-dimetoksitetragidroizoxinolinlar bilan ta’sirlashuvi natijalari keltirilgan.Reaksiya

metanolda 4-5 soat davomida qaynatish bilan olib borilgan. Barcha birikmalar boshlang‘ich izoxinolinlarga bog‘liq bo‘lmagan holda kristall ko‘rinishda yuqori unumda (70-82 %) ajratilgan.



2.9. Izoxinolinlar biologik faolliklarini o‘rganishning asosiy yo‘nalishlari

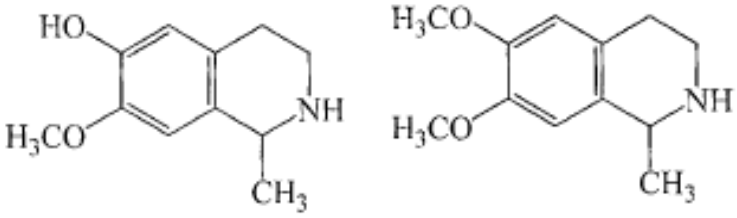
Hozirgi vaqtda asosiy e’tibor zarur farmakalogik xossali birikmalar olish maqsadida izoxinolin hosilalarining struktur modefikatsiyasi hamda sinteziga qaratilgan. Faollik turlarini o‘rganishning asosiy yo‘nalishlari bevosita birikma tuzilishi bilan bo‘liq bo‘lib, molekula tuzilishi murakkablashishi tartibida o‘rganish ancha o‘rinli hisoblanadi. Tirozin, dofamin, noradrenalin, larning tuzilishi formulalaridan ko‘rinib turibdiki ularning strukturasida umumiy fragment β-feniletilamin qoldig‘i mavjud.



MAT (markaziy asab tizimi) faoliyatiga ta’sir etuvchi, dafanenergik jarayonlarda qatnashuvchi oddiy tuzilishli almashinmagan 1,2,3,4-tetragidroizoxinolinlar ustida ko‘p sonli tadqiqotlar o‘tkazilgan [63].

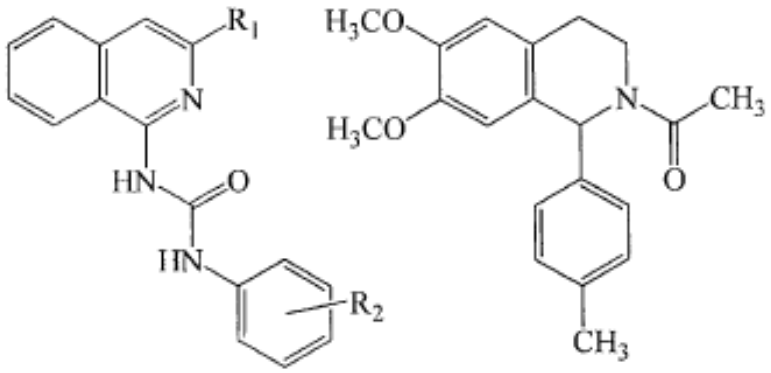
Birinchi holat bo‘yicha almashinmagan izoxinolinlar monoaminoksidazalar (MAO) ingibitorlari bo‘lishi mumkin. Shuningdek, ayrim holatlarda N-almashingan izoxinolinlar ham aminotransferaza ingibirlash hisobiga antigistonin ta’sir ko‘rsatishi mumkin [64].

1 holatda almashingan izoxnolinlar hosilalari keng tarqalgan va turli-tuman bioligik faolliklarni namoyon etadi. Ular orasida antidepressiv, o‘smaga qarshi [65], viruslarga qarshi, antigelment, malyariyaga qarshi, shuningdek spazmalitik, gemostatik [66] antikonvulsant [67] va b,q.xossali moddalar uchraydi. Tibbiyot amaliyotida qo‘llaniladigan salsolin va salsolidin 1-metilalmashingan izoxinolin hosilalari hisoblanadi.Salsolin qon tomirlarini kengaytirib, arterial qon bosimini pasaytiradi. U kam zaharli bo‘lib nojo‘ya ta’sir ko‘rsatmaydi. Salsolidin ta’sir xususiyati bo‘yicha salsolinga o‘xshaydi, lekin nisbatan kuchsiz.



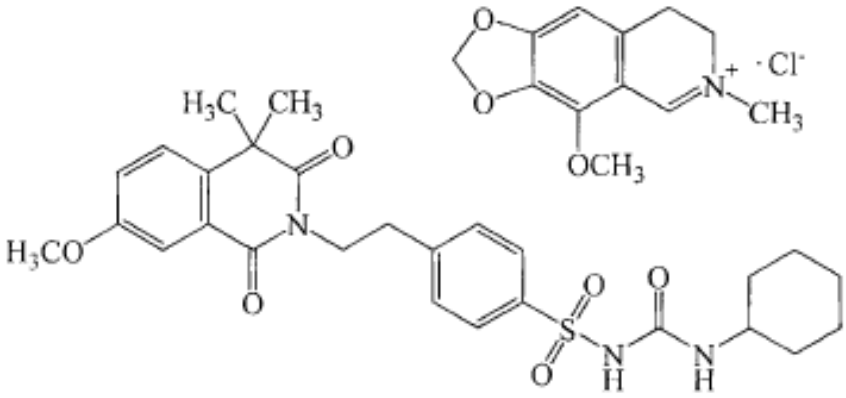
Asosiy e’tibor izoxinolin hosilalarining gipotenziv faolligiga qaratilgan. Shu sohadagi ishlarni ko‘rsatish mumkin. Bunda mualliflar 1-almashingan izoxinolin hosilalarini sintezlab xususiyatlarini o‘rganishgan. 1 holatda amid, benzil guruhlariga ega bisizoxinolinlarning ham gipotenziv va qon tomirlarini kengaytiruvchi ta’sirlari kuzatilgan.

Izoxinolinlar orasida adenozin A_3-reseptorlari antaganistlari mashhur bo‘lib ular o‘z navbatida neyromator kasalliklarda tirishishga qarshi ta’sir ko‘rsatadi.Izoxinolinlar antiaritmik vositalar, bronxolitiklar ham hisoblanadi. N-almashingan izoxinolin hosilalarida turli ko‘rinishdagi farmakalogik faolliklar kuzatiladi [64]. Msalan, birikmalar α_2-adrenoreseptorlar antogonisti hisoblansa, tarkibida shunday fragment tutganlari P-adrenolitik sifatida qaraladi.

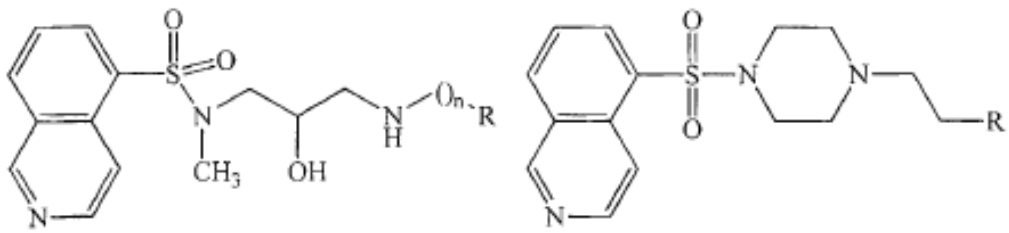


Tibbiyot amaliyotida kotarniu gidroxlorid qo‘llaniladi. Ularning ta’sir mexanizmi ichki a’zolar asosan bachadon silliq muskullari tonusini oshirish bilan bog‘liq. Yallig‘lanish jarayonlari va fibroma asosidagi bachadon qon ketishlarida qo‘llaniladi [66].

N-almashingan hosilalar asosida dori vositalari glikvidon bo‘lib, me’da osti bezi P-hujayralari (insulositlar)ni stimullash hisobiga gipoglikemik ta’sirini namoyish etadi, insulin mobilizatsiyasini kuchaytiradi,qonda glukugon darajasini pasaytirib, to‘qima va muskullarda insulin reseptorlari miqdorini oshiradi.



Ayrim moddalar izoxinolinlar asosida 3,4,5-holatlarda o‘rinbosar saqlaganlarini alohida ta’kidlash zarur. 5-holatga sulfonilamidli fragmentni kiritish malyariyaga (bezgak) qarshi samaraga olib keladi (38,39-birikmalar) [65].



Bu xossa 3-holatda aromatik ftor- va aminosaqlagan qoldiqlar bo‘lganda ham saqlanib qoladi, 4-holatda okso-guruhning bo‘lishi bu ta’sirni kuchaytiradi. Bundan

tashqari bezgakka qarshi xossali izoxinolin hosilalarini antiprotozoy ta’siriga ham ega.

Mualliflar [68] ishda izoxinolin qatori alkaloidlarining immunotrop faolliklarini qiyosiy o‘rganishgan.

III. NATIJALAR MUHOKAMASI

Tarkibida geteroatomlar saqlagan tabiiy va sintetik geterosiklik birikmalar asosida tadqiqotlar olib borish keng tarqalmoqda. Buni so‘nggi yillarda chop qilinayotgan ilmiy maqolalar va dissertatsiya ishlarida ham ko‘rishimiz mumkin.

Hozirgi vaqtda asosiy e’tibor zarur farmakalogik xossali birikmalar olish maqsadida izoxinolin hosilalarining struktur modefikatsiyasi hamda sinteziga qaratilgan. Faollik turlarini o‘rganishning asosiy yo‘nalishlari bevosita birikma tuzilishi bilan to‘liq bo‘lib, molekula tuzilishi murakkablashishi tartibida o‘rganish ancha o‘rinli hisoblanadi. Birinchi holatda almashingan izoxnolinlar hosilalari keng tarqalgan va turli-tuman bioligik faolliklarni namoyon etadi. Ular o‘smaga qarshi, viruslarga qarshi, antigelment, malyariyaga qarshi, shuningdek spazmalitik va b.q. xossali moddalar uchraydi.

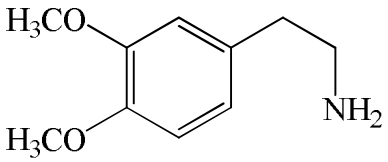
Mazkur yo‘nalishda olib borilayotgan tadqiqotlar ham nazariy ham amaliy jihatdan muhimdir. Bunga misol qilib qator yillar davomida Organik va noorganik kimyo kafedrasi va O‘simlik moddalari kimyosi institutida izoxinolin alkaloidlari va ularning turli hosilalari asosida keng miqyosidagi ilmiy-amaliy tadqiqotlar olib borilmoqda va natijada juda muhim qonuniyatlar topilishi bilan bir qatorda sintez qilingan birikmalar asosida turli biologik faolliklar topilmoqda.

Biz olib borayotgan sintezlarimizda boshlang‘ich mahsulot sifatida gomoveratrilamin va bir, ikki asosli kislotalarni olgan edik [69,70]. Bir asosli kislotalar bilan olib borilgan sintezlarda olingan mahsulotlarning farmakologik faolligi R- radikalining ya’ni undagi uglerodlar sonining ortib borishi bilan faollikning ham ortishini kuzatgan edik. Ikki asosli karbon kislotalar bilan olib borilgan sintezlarda esa diizoxinolin qatori hosilalari olingan edi. Bu qator alkaloidlarida ham ikki asosli karbon kislota molekulasidagi metilen guruhlarining ortib borishi bilan ularning biologik faolligi ham ortishi kuzatildi. Bulardan tashqari oxirgi yillarda imidazol halqali karbon kislotalar asosida ham sintezlar olib borilgan [71,72].

Biz yanada biologik faolligi kuchliroq ifodalangan ya’ni turli farmakologik ta’sirga ega bo‘lgan preparatlarni olish maqsadida molekulasida piridin qoldig‘i

saqlagan nikatin kislota asosida bosqichli sintezlarni amalga oshirdik. Birinchi bosqich kondensatlanish reaksiyasi, ikkinchi bosqich esa sikllanish reaksiyasi hisoblanadi. Sikllanish reaksiyasi Bishler –Napiralskiy reaksiyasi sharoitida olib borildi.

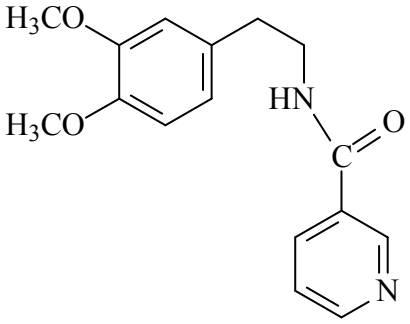
3,4-dimetoksifeniletilamin yoki gomoveratrilamin boshlang‘ich mahsulot sifatida olingan. Bu sintezlar O‘MKI xodimlari bilan birgalikda amalga oshirildi.



feniletilamin

Molekulyar massasi Mr=181 g

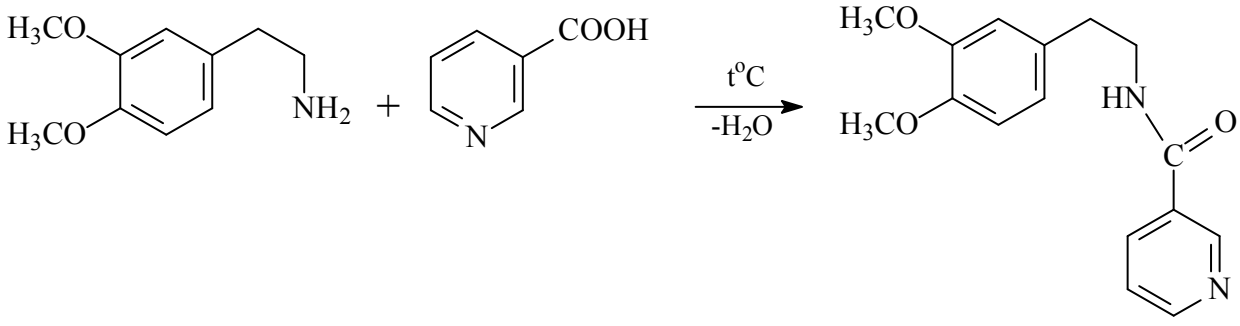
3.1. N-(3,4-Dimetoksi-β-feniletil)-*m*-piridinamidning olinishi



Reaksiyaning birinchi kondensatlanish bosqichi quyidagi tartibda olib borildi. Kolbaga gomoveratrilaminni metanolda eritib ustiga izonikotin kislota qo‘shib aralashtirildi. Aralashma moy hammomida 180°C da 4 soat qizdirildi. Reaksiyani borishi YuQX yordamida tekshirib borildi. Qizdirish tugagach xloroformda eritilib dastlab HCl eritmasi bilan yuvildi. Reaksiyaga kirishmay qolgan aminni reaksion aralashmadan chiqarib yuborish uchun neytral muhitga o‘tguncha distillangan suvda, so‘ngra NaOH eritmasi bilan yuvildi. Reaksiyadan ortib qolgan kislotani reaksion aralashmadan chiqarib yuborish uchun, qaytadan neytral muhitga o‘tguncha distillangan suvda yuvildi. Kislota bilan yuvilganda bizga kerakli bo’lgan izonikatin amid kislota qavatiga o’tib ketdi bunga sabab piridin halqasidagi azot atomining juft eliktronlar xisobiga HCl bilan ta’sirlashib tuz hosil qilib qoldi. Kislota qavatiga o’tib ketgan izonikatin amidni aralashma tarkibidan qaytadan organik erituvchiga o’tkazib olish uchun kislotali aralashma NH_4OH qushib ishqoriy muhitga o’tkazildi va ajratish varonkasida xloroformda yuvib olindi. Xloroform haydaldi, asetonda quritilib, kristal tushgunga qadar asetonda qoldirildi, kristallandi va kristall filtrlab olindi.

Amidning strukturasi IQ- va PMR- spektrlari orqali isbotlandi.

Reaksiya quyidagi sxemada olib borildi:

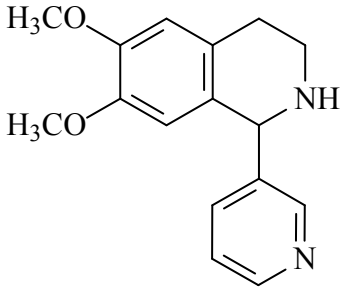


Izonikatinamidning IQ- spektrida xarakterli signallari 1648 sm^{-1}, 2935 sm^{-1} va 3319 sm^{-1} sohada yutilish chiziqlariga ega bo'lib, ular quyidagi guruhlarning CO, Ar-C va NH- valent tebranishi hisobiga yuzaga chiqadi.

Izonikatinamidning ^{1}H YaMR- spektrida α-holatdagi metilen guruhning ($-CH_2$) protonlari 2,86 m.u. da ikkita protonli triplet ko'rinishida (J=6,8), 3,68 m.u. da β-holatdagi protonlar ikkita protonli triplet ko'rinishida (J=5,8) kuzatiladi. Aromatik halqadagi – O – CH_3 guruhlar (C-3 va C-4) 3 ta protonli singlet ko'rinishida 3,81 m.u. va 3,83 m.u. kuzatiladi. Aromatik halqadagi protonlar H-2, H-5 va H-6 ga tegishli quyidagi sohada kuzatiladi. 6,72 m.u. bitta protonli, H-2; 6,73 m.u. bitta protonli dublet-dublet J=2, 8, H-6; 6,79 m.u. bitta protonli dublet J=8, H-5.

Piridin halqasidagi protonlar H-2', H-4', H-5' va H-6' ga tegishli signallar quyidagi sohalarda kuzatildi. 7.32 m.u. bitta protonli ddublet-dublet J=1.4, 4.8, 7.8, H-6'; 8.02 m.u. bitta protonli dublet-triplet J=2, 7.8, H-5'; 8.65 m.u. bitta protonli dublet-dublet J=1.5, 4.8, H-4'; 8.84 m.u. bitta protonli dublet J=2, H-2'.

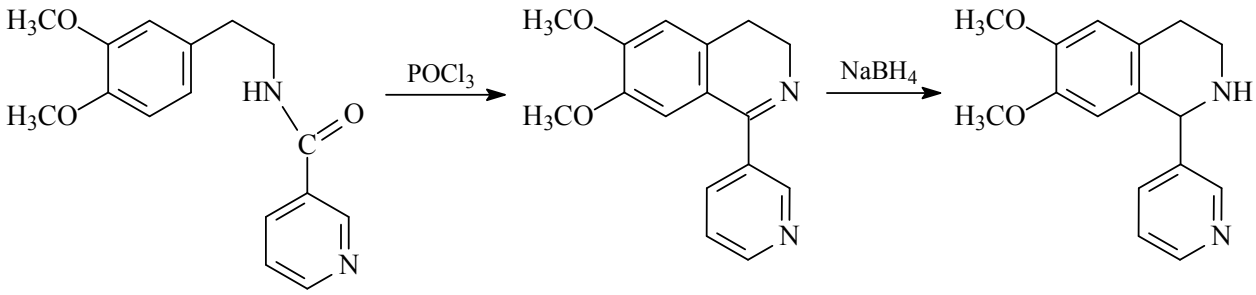
3.2. 6,7-Dimetoksi-1-(piridin-3-il)-1,2,3,4-tetrgidroizoxinolinning olinishi



Sikllanish reaksiyasini olib borish uchun suvni tortib oluvchi reagent sifatida $POCl_3$ ishlatiladi. Nikotinamid ustidan $POCl_3$ qo‘shildi va reaksion aralashma suvli hammomda qaynatildi. Reaksiyani borishini YQX yordamida tekshirib borildi. Qizdirish tugagach reaksion aralashma muzda eritilib temperatura 0-5^oC da ushlagan holda ishqoriy muhitga utgunga qadar 25% NH_4OH eritmasidan qushildi, so‘ng ajratish varonkasida xloroform qavatga utkazildi va qurutildi, metanolda eritilib $NaBH_4$ ishtirokida temperatura 0-5^oC da ushlagan holda qaytariladi ya’ni 3,4-digidroizoxinolindan, tetragidroizoxinolingacha. Suvda eritilib xloroformda yuvib olindi so‘ng xloroform haydaladi va quritildi. Reaksiya mahsuloti atsetonda kristallga tushirildi va filtrlab olindi.

Olingan tetragidroizoxinolin tozalanib, uning tozaligi YuQX yordamida tekshirib ko‘rildi. Tetragidroizoxinolinning strukturasi IQ- va YaMR- spektrlari orqali isbotlandi..

Reaksiya quyidagi sxemada olib borildi:



Izonikatin kislota tetragidroizoxinolinining IQ- spektrida xarakterli signallari 1610 sm^{-1}, 2916, 2816, 2586, 2516 sm^{-1} va 3346 sm^{-1} sohada yutilish chiziqlariga ega bo’lib, ular quyidagi guruhlarning ArC=N, Ar-C va NH- valent tebranishi hisobiga yuzaga chiqadi. Pikolin kislota tetragidroizoxinolinining ^1H YaMR- spektrida 3-

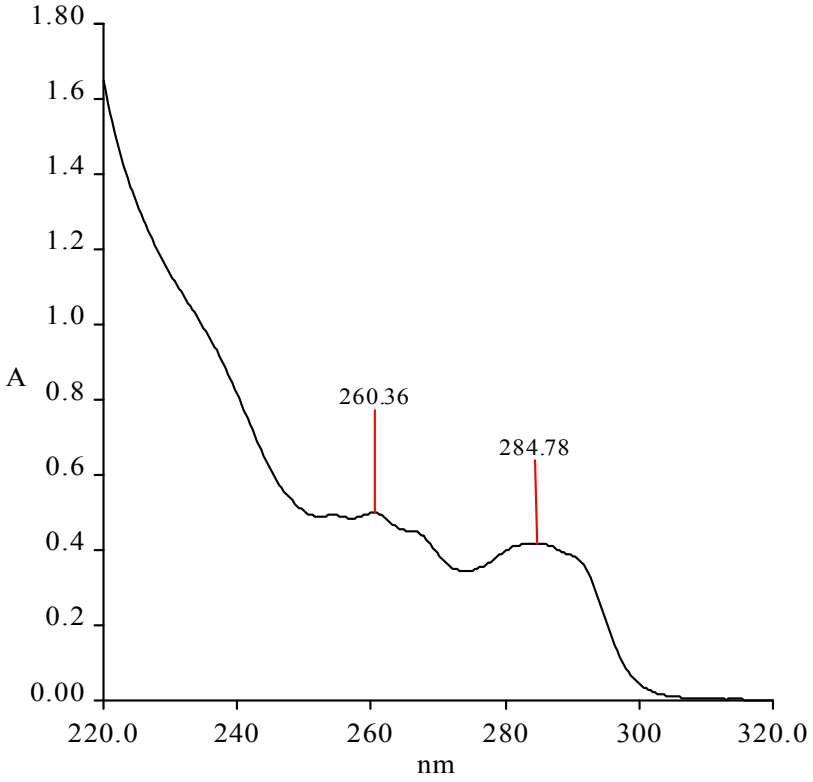
holatdagi metilen guruhning (-CH_2-) protonlari 3,40 m.u. da va 3,08 i 3,16 m.u. da 4-holatdagi protonlar kuzatiladi. H-1 holatdagi protonning signali 5,05 m.u. kuzatildi. Aromatik halqadagi – O – CH_3 guruhlar (C^3 va C^4) 3 ta protonli singlet ko‘rinishida 3,56 m.u. va 3,77 m.u. kuzatiladi. Aromatik halqadagi protonlar H-5 va H-8 ga tegishli quyidagi sohada kuzatiladi. 6,41m.u. bitta protonli singelit H-8; 6,85 m.u. bitta protonli singelit H-5;

Piridin halqasidagi protonlar H-2', H-3', H-5' va H-6' ga tegishli signallar quyidagi sohalarda kuzatildi.

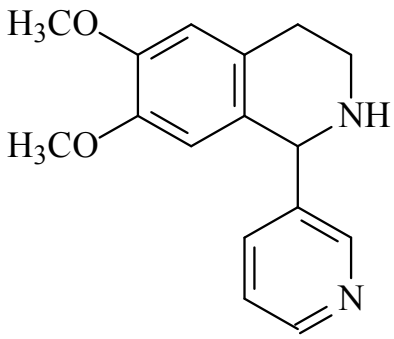
8.08 m.u. bitta protonli dublet-dublet J=.5.8, 8, H-4'; 8.50 m.u. bitta protonli dublet-treplit J=1.5, 8, H-5'; 8.88 m.u. bitta protonli dublet J=6, H-6'; 8.89 m.u. bitta protonli keng singelit, H-2'.

Масс-спектре hosil bo’lgan palasa m/z 293 $[M+Na]^+$ и 271 $[M+H]^+$.

6,7-Dimetoksi-1-(piridin-3-il)-1,2,3,4-tetrgidroizoxinolinning UF sipiktrida yutilish palasalari quyidagicha olbastdlarda ko’zatilgan 260,36 nm va 284,78 nm.



Olingan tadqiqot natijalarininh farmakalogik aktivligi PASS (*Prediction of Activity Spectra for Substances*) dasturida kompyuter bashoratlash natijasi



☐ All ☐ Pa>Pi ☐ Pa>0,3 ☐ Pa>0,7

0,893	0,003	Nicotinic alpha4beta4 receptor agonist
0,887	0,004	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,887	0,006	5 Hydroxytryptamine release stimulant
0,863	0,004	Nicotinic alpha2beta2 receptor antagonist
0,811	0,015	Antineurotic
0,719	0,005	Oxygen scavenger
0,712	0,038	Nootropic
0,637	0,012	MAP kinase stimulant
0,644	0,048	Fibrinolytic

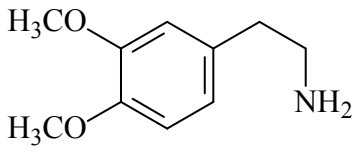
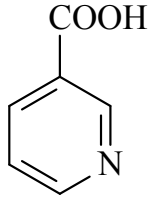
IV. TAJRIBAVIY QISM

Olingan reaksiya mahsulotlari birinchi bosqichda kislota amidi va ikkinchi bosqichda siklizatsiya va degidrogenlanish mahsulotlari hamda qaytarilish mahsulotlarining ham fizik–kimyoviy konstantalari va spektral tahlili o‘rganildi. Olib borilayotgan sintez va sintez mahsulotlari yupqa qatlamli xromatogrammada nazorat qilib turildi. Erituvchilar sistemasi sifatida xloroform – metanolni har xil nisbatlarda olindi. Adsorbent sifatida silikogelning L5/40 markasini (13% li gips) suvda tayyorlab shisha plastinkalarda maxsus qurilma yordamida yotqizib chiqildi. Erituvchilar sistemasi sifatida quyidagilar olindi: sistema (xloroform-metanol 4:1).

Reaksiya mahsulotlarini xromatogrammada aniqlash uchun ochuvchi reagent sifatida UB lampa, yodli kamera va Dragendorf eritmasidan foydalanildi.

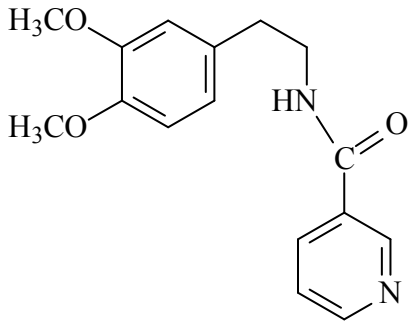
Natijalar muhokamasi qismida ularning PMR spektrlari o‘rganildi. Bunda barcha tozalash, qayta kristallashlardan keyin qolgan reaksiya mahsuloti induvidual bo’lgani uchun spektral tahlil uchun ishlatildi. Ayrim reaksiya mahsulotlaridan farmakologik tekshiruvlar uchun namunalar tayyorlandi.

Reaksiya uchun olingan reaktivlar fizik–kimyoviy konstantalari

Strukturasi	Tarkibi	Molyar massasi	Kimyoviy nomlari
	$C_{10}H_{15}O_2N$	181	3,4-dimetoksi-β-feniletilamin (gomoveratrilamin)
	$C_6H_5O_2N$	123	*m*-piridin kislota
$CHCl_3$	$CHCl_3$	119,5	Xloroform
CH_3OH	CH_4O	32	Metanol
CH_3-CO-CH_3	C_3H_6O	58	Atseton
$POCl_3$	$POCl_3$	153,5	Fosforoksixlorid
HCl	HCl	36,5	Xlorid kislota
NaOH	NaOH	40	Natriy gidroksid
$NaBH_4$	$NaBH_4$	38	Natriyborgidrid
Silikogel	-	-	Silikogel
Dragendorf eritmasi	-	-	Dragendorf eritmasi

4.1. N-(3,4-Dimetoksi-β-feniletil)-*m*-piridinamid, $C_{16}H_{18}N_2O_3$ **sintezi**.

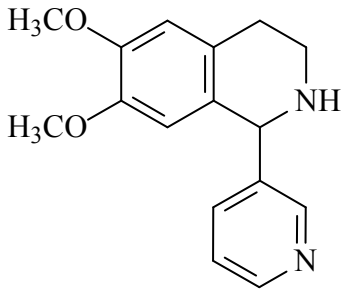
Kolbaga 0.38 g (2,1 mmol) gomaveratrilaminni 5 ml metanolda eritib ustidan 0.28 g (2,3 mmol) izonikotin kislota solib aralashtirildi natijada kolba bir oz qiziydi so‘ng aralashma 180°C da 4 soat qizdirildi. Metanolda eritilib HCl qushib xlorgidratga aylantrildi va quritildi, asetonda kristal tushirildi va feltrlab olindi. Unumi 81% (0,49 g), yog’simon, R_f 0,82 (sistema xloroform:metanol 4:1).



IQ-spektr (pilyonka, *ν*, см$^{-1}$): 3319 (NH), 2935 (Ar-C), 1648 (N -C=O), 1592, 1546, 1516, 1465, 1418 (C=C). ^{1}H YaMR spektr (400 МГц, $CDCl_3$, *δ*, м.д., J/Гц): 2.86 (2H, т, J=6.8, Hα); 3.68 (2H, кв, J=5.8, Hβ); 3.81 (3H, с, OCH_3); 3.83 (3H, с, OCH_3); 6.32 (1H, NH); 6.72 (1H, с, H-2); 6.73 (1H, дд, J=2, 8, H-6); 6.79 (1H, д, J=8, H-5); 7.32 (1H, ддд, J=1.4, 4.8, 7.8, H-6'); 8.02 (1H, дт, J=2, 7.8, H-5'); 8.65 (1H, дд, J=1.5, 4.8, H-4'); 8.84 (1H, д, J=2, H-2').

4.2. 6,7-Dimetoksi-1-(piridin-3-il)-1,2,3,4-tetrgidroizoxinolin, $C_{16}H_{18}N_2O_2$ **sintezi.**

Kolbaga 0,4 g (1,4 mmol) *m*-piridinamid 0,6 ml $POCl_3$ qo‘shib aralashtirildi va reaksion aralashma 6 soat teskari sovutgich o’rnatilgan holda suv hammomida qaynatildi. Reaksiyani borishini YuQX yordamida nazorat qilib borildi. Reksiya tugagach reaksion aralashma muzda eritilib pH=9 ga kelguncha 25% NH_4OH eritmasidan qushildi va xloroform qavatga o‘tgazildi, so‘ng quritildi, 50 ml metanolda eritib temperaturani 0–5°C da ushlagan holda 0,04 mol $NaBH_4$ bilan qaytarildi ya’ni 3,4-digidroizoxinolindan tetragidroizoxinolingacha. Metanol haydaldi, quritildi va suvda eritilib, xloroform qavatiga o‘tkazildi. Xloroform qavati haydaldi va quritildi. Reaksiya mahsuloti asetonda kristall tushirildi va filtrlab olindi. Unumi 72% (0,14 g), t.suy. xlorgidrat 176-179°C (aseton), R_f 0,51 (sistema xloroform:metanol 4:1).



IQ-spektr (KBr *ν*, cm^{-1}): 3346 (NH), 2916, 2816, 2586, 2516 (Ar-C), 1611, 1581 (ArC=N), 1520, 1466, 1443, 1409 (Ar-H).

^{1}H YaMR spektr (400 МГц, $CDCl_3$, *δ*, м.д., J/Гц): хлоргидрата: 3.08 (1H, м, H-4а); 3.16 (1H, м, H-4б); 3.40 (2H, м, H-3); 3.56 (3H, с, OCH_3); 3.77 (3H, с, OCH_3); 6.08 (1H, с, H-1); 6.41 (1H, с, H-8); 6.85 (1H, с, H-5); 8.08 (1H, дд, J=5.8, 8, H-4'); 8.50 (1H, дт, J=1.5, 8, H-5'); 8.88 (1H, д, J=6, H-6'); 8.89 (1H, уш.с, H-2').

V. XULOSALAR

1. Farmakalogik faolligi, izoxinolin va xinozolin-izoxinolin alkaloidlarining sintez yo‘llari o‘rganildi.

2. Kondinsatlanish va sikllanish reaksiylari natijasida amid va tetragidroizo-xinolin hosilasi sintez qilindi.

3. Sintez qilib olingan mahsulotlarni IQ-, PMR H^1 va mass spektrlari asosida struktura tuzilishi o’rnatildi.

4. Olingan amid va tetragidroizoxinolinning farmakologik aktivligi aniqlandi.

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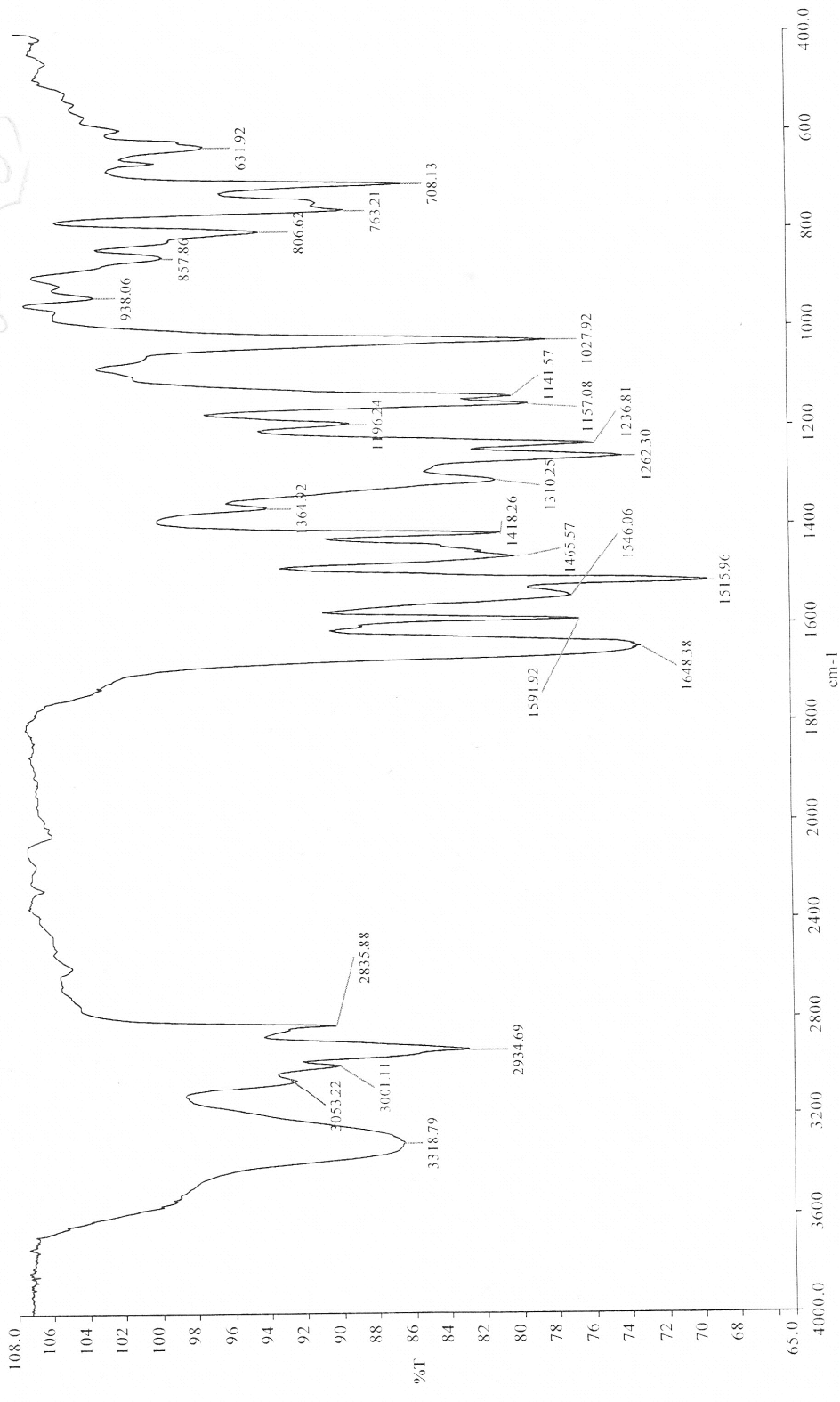
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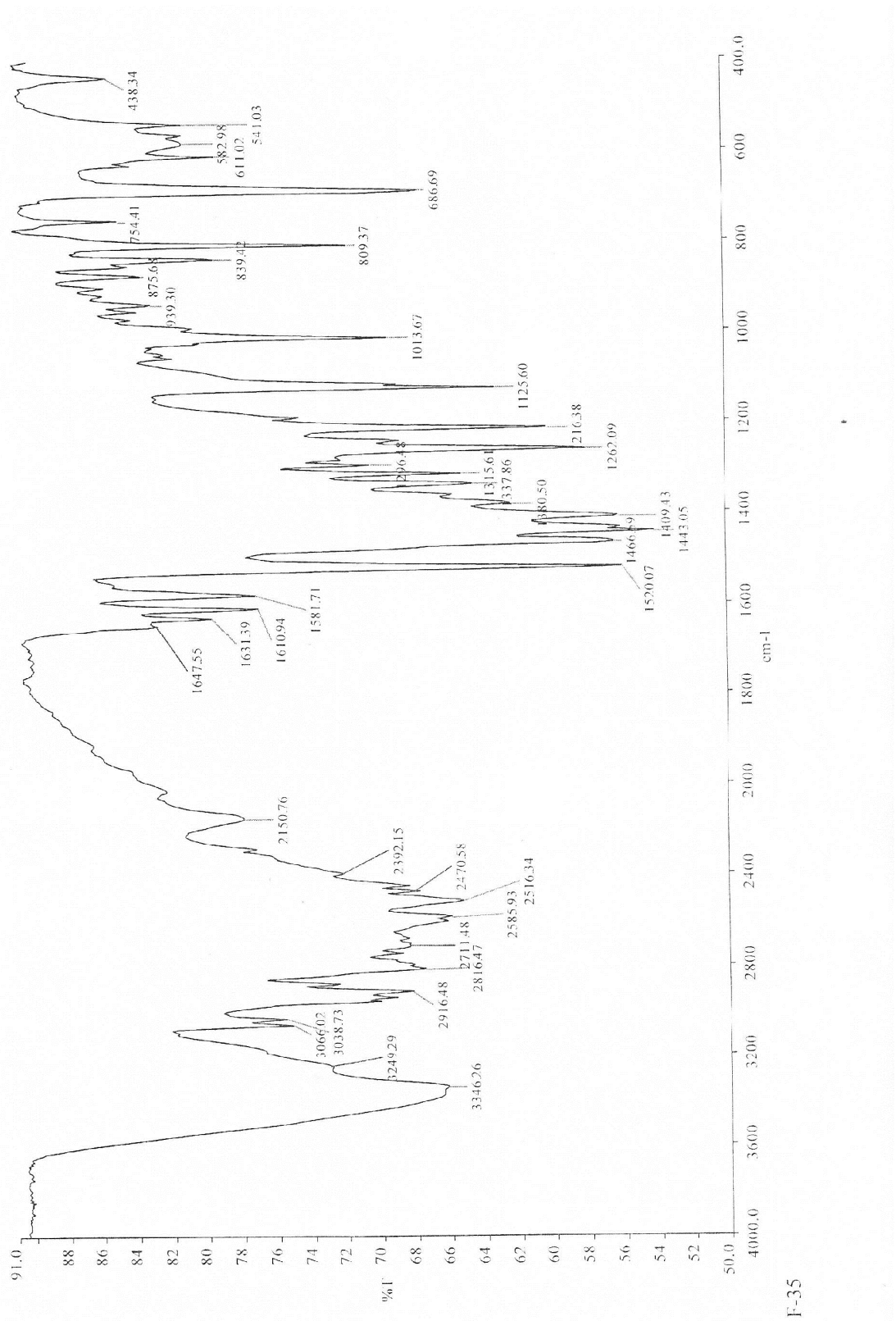
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Display Report

Analysis Info

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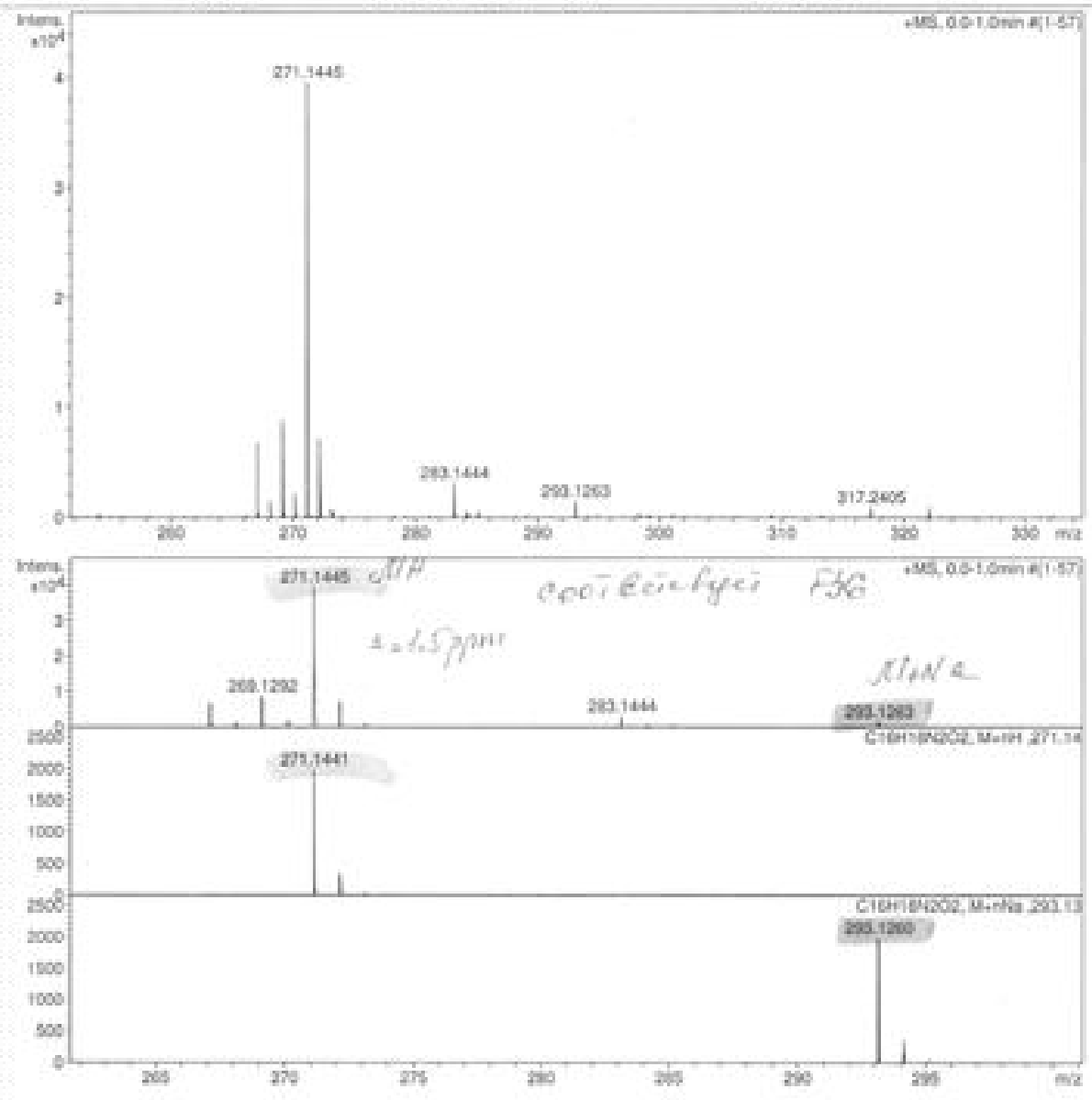

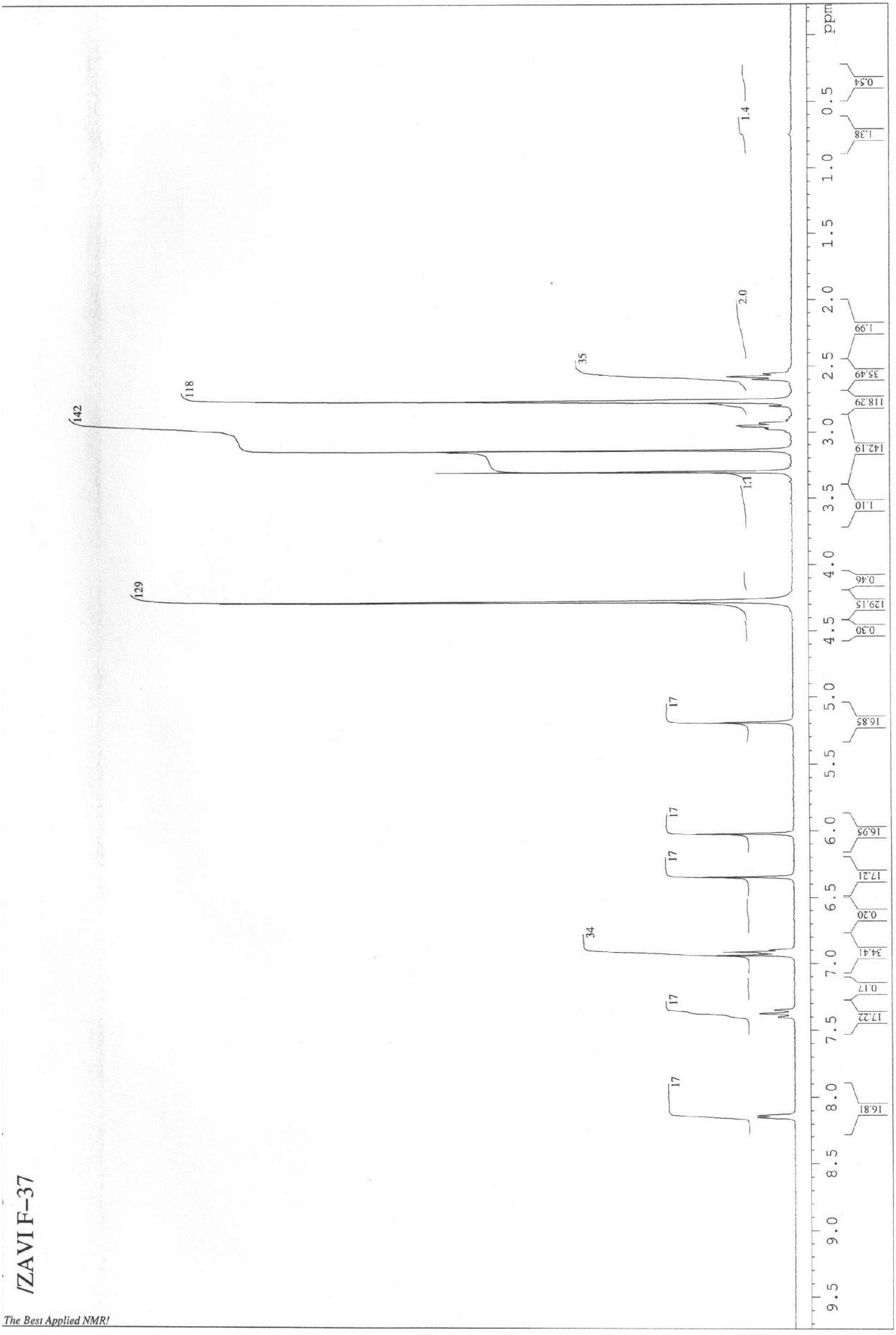
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